Stereoselective Synthesis of 5-Substituted Pyrrolo[1,2-c]imidazol-3-ones. Access to Aldosterone Synthase Inhibitors and Chiral Precatalysts

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Abstract

Compounds containing the pyrrolidine moiety are key substructures of compounds with biological activity and organocatalysts. In particular, annulated chiral pyrrolidines with alpha stereogenic centers have aldostereone synthase inhibition activity. In addition, 5-substituted pyrroloimidazol(in)ium salts precursors to *N*-heterocyclic carbene (NHC) precatalysts are rare due to a lack of convenient synthetic routes to access them.

In this thesis is described a rapid synthesis of NHC precursors and a possible route to 5-substituted pyrroloimidazole biologically active compounds. The method involves the preparation of chiral saturated and achiral unsaturated pyrrolo[1,2-c]imidazol-3-ones from *N*-Cbz-protected *t*-Butyl proline carboxamide. The resulting starting materials may be used to prepare the target chiral annulated imidazol(in)ium products by a two-step sequence involving first stereoselective lithiation-substitution, followed by $POCl_3$ induced salt formation.

Acknowledgments

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To my parents, brother and dearest friends: thanks for being supportive every second of my life; especially to my family, for providing me with all the necessities which have enabled me to pursue higher education.

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Abbreviations

Ac	acetyl
Ar	aryl
b	broad
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Bu	butyl
cat	catalyst
Cbz	carbobenzyloxy
COSY	correlation spectroscopy
d	doublet
dba	dibenzylidene acetone
DBU	1,5-diazabicyclo[4.3.0]non-5-ene
de	diastereomeric excess
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
ee	enantiomeric excess
EI	electron impact
EIMS	electron impact mass spectrum
EWG	electron withdrawing group
FAB	fast-atom bombardment
equiv	equivalents
h	hours
KHMDS	potassium hexamethyldisilazan
KO*t*-Bu	potassium tert-butoxide
HRMS	high resolution mass spectrum
IR	infrared
$LiAlH_4$	lithium aluminum hydride
m	multiplet
mes	mesityl
$MgSO_4$	magnesium sulfate
mp	melting point
MTBE	methyl *tert*-butyl ether
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
HSQC	heteronuclear single quantum coherence
NOE	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
OAc	acetoxy
Ph	phenyl
POCl3	phosophoryl chloride
PP	polyproline
q	quartet

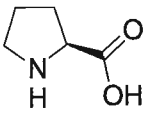
rac	racemic
rt	room temperature
s	singlet
t	triplet
THF	tetrahydrofuran
TMS	trimethylsilyl
t_R	retention time

1. Introduction:

Pyrrolidines are a common structural motif found in natural products and biologically active molecules, including opioid receptor ligands, natural amino acids, and chiral pyrroloimidazoles.[1] This structural motif has also captured the interest of many organic chemists. Besides serving as crucial reagents or reactants in many organic reactions, pyrrolidine-containing molecules have been established as important to catalysis and asymmetric reactions, wherein selective induction of chirality may be observed.[1] The following section will briefly introduce pyrrolidine-containing biologically active molecules, naturally occurring molecules, and chiral reagents.

1.1 The Pyrrolidine Moiety in Natural Products and Biologically Active Compounds

A commonly encountered pyrrolidine in nature is the natural amino acid L-proline **1**. Being the only heterocyclic amino acid in nature, L-proline plays a very important role in the secondary structures of proteins. Due to its cyclic structure, proline is commonly observed in a given protein where a β-turn is located, which contributes to the rigidity of the protein, and in turn can affect biological activities of enzymes.[2,3,4] The discovery of polyproline II helices as the dominant motif in proline-rich sequences has led to rapid research in analogues of proline.[2] It is believed that the PPII helices plays an important role in protein-protein interactions by altering conformations through incorporation of analogues of proline (usually by solid phase chemistry), which may affect the bioactivity of the protein.[25]



1

Figure 1. *L*-Proline

Many 2,5-disubstituted pyrrolidine compounds have been extracted from plants, animals and microorganisms. Unfortunately, the quantities isolated are usually very limited, thus the biological activity and mechanisms of action of many of these compounds have not been studied.[1] Of the molecules studied, some have displayed interesting properties such as the ability to inhibit acetylcholinesterase (**2**),[6] and the ability to ligate with the opioid receptor (**3**).[1] Another famous pyrrolidine compound is a molecule that is inhaled by smokers, nicotine (**4**).

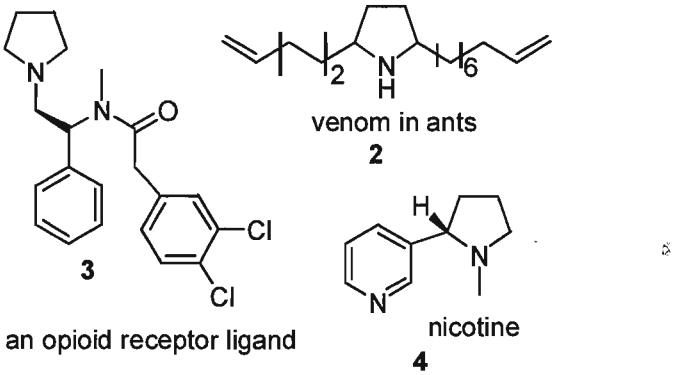


Figure 2. Examples of pyrrolidine-containing biologically active compounds

Chiral α-arylated pyrrolidine molecules fused with imidazole (**5, 6**) are also reported in the literature and have been recognized for their inhibitory activities against aldosterone synthase and aromatase.[7] Thus, they may be utilized to treat disorders or disease associated with these two enzymes (e.g., hypokalemia, hypertension, congesitive

heart failure, and arial fibrillation or renal failure).[8] However, these potential drugs were synthesized only as racemates and require chiral stationary phase HPLC separation.

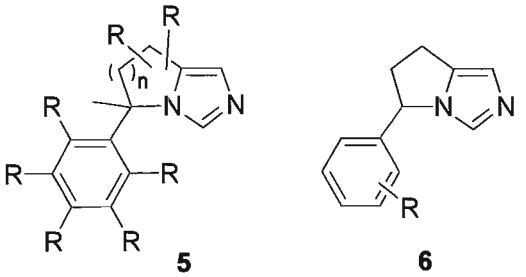


Figure 3. Chiral pyrroloimidazoles

1.2 Catalysts Containing the Pyrrolidine Structural Motif

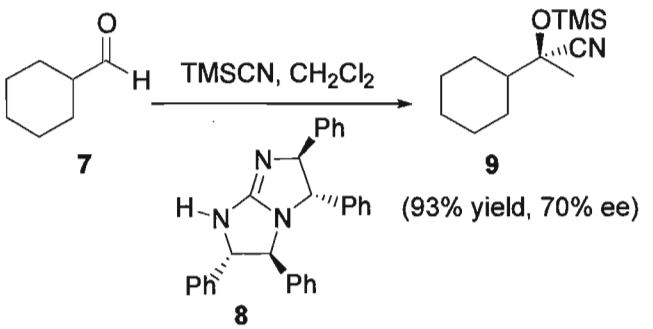
1.2.a. Guanidines

Synthetic guanidine analogues are considered to be environmentally friendly catalysts since this functional group is widely observed in biological systems.[9] Due to their resonance within the three nitrogens, the guanidine functionality is generally considered to be one of the strongest organic bases (pKa of 12.5).[9] This property should allow guanidines to catalyze base-mediated organic reactions. Unfortunately, their application in catalysis is not well studied due to the lack of synthetic methods to prepare them which may be due to safety issues associated with their synthesis. In the classic method, preparation usually involves the use of cyanide reagents, which are extremely toxic, dangerous and not environmentally friendly.[10]

A prominent researcher in this field, Ishikawa, has prepared guanidines which incorporate a fused pyrroloimidazoline structural motif, prepared by nucleophilic addition of an amine to an imidazolinium intermediate.[11-14] Their activities and applications were

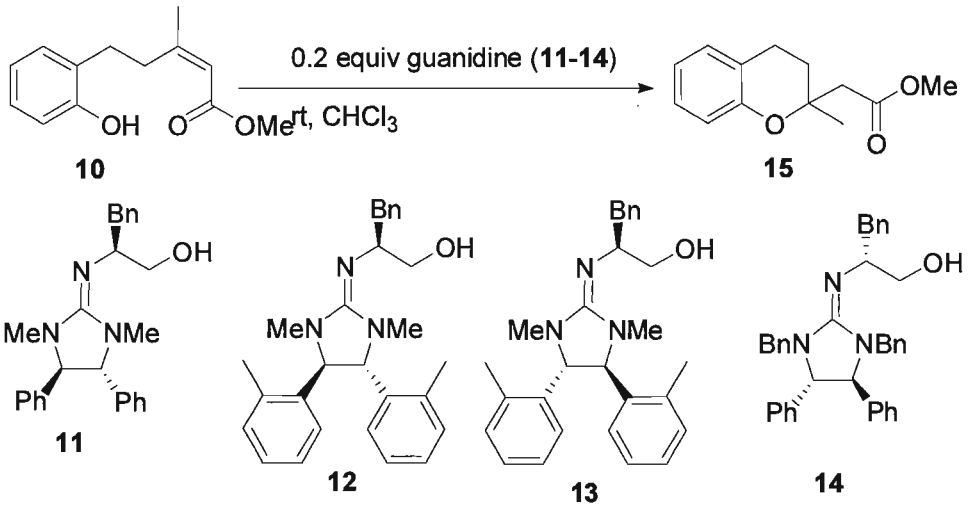
explored in various reactions, such as the Michael addition and the trimethylsilylcynanation of carbonyl compounds,[15] in which they were proven to be effective.[16]

In the asymmetric trimethylsilylcyanation of carbonyl groups, guanidines similar to **8** have catalyzed this reaction in over 90% yield with low to moderate enantiomeric excess (ee). One of the best results was with guanidine **8** in the reaction with cyclohexylaldehyde **7** to give **9** in 93% yield and 70% ee.[15]



Scheme 1. Asymmetric trimethylsilylcyanation of carbonyl compounds[15]

Among other successful applications, guanidines **11-14** have been employed in the construction of the chiral backbone of vitamin E (**15**), involving a 2,2-disubstituted chromane skeleton **15**. From **Scheme 2** and **Table 1**, the best results were achieved using **12** to give **15** in 80% ee at 0 °C (but only with 41% yield). With guanidines **13** and **14**, there were low enantioselectivities and yields.[16]



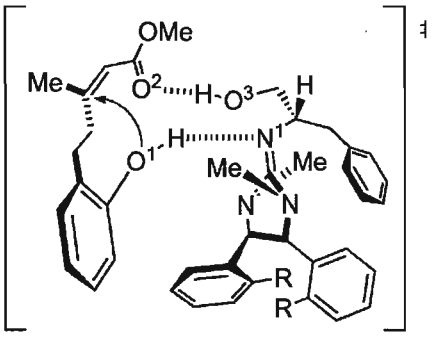
Scheme 2. Guanidines in Michael addition[16]

Table 1. Results of the Oxa-Michael addition[16]

Guanidine	time (d)	yield (%)	ee (%) (*config*)
11	2	75	71 (*R*)
12	2	83	76 (*R*)
12[a]	2	41	80 (*R*)
13	2	53	29 (*R*)
14	7	39	23 (*S*)

[a]Reaction was carried out at 0 °C.

The alcohol function of guanidines **11-14** provides better enantio-induction as described by Ishikawa et al. In their speculation, the transition state **16** between guanidine and substrate not only allows for hydrogen bonding between the alcohol of the guanidine to that of carbonyl of the substrate, but also allows for hydrogen bonding between the substrate's phenol and the guanidine nitrogen. This model invokes a 15-membered transition state that allows the substrate to avoid a methyl group on the guanidine nitrogen, resulting in a preferential attack of only one face of the substrate (**Figure 4**).[16]



TS
(*re*-face attack)

16

Figure 4. Transition-state for guanidine **16**[16]

1.2.b. Chiral Phosphites and Phosphorodiamidites

Chiral monodentate phosphites and phosphorodiamidites are a relatively new class of ligands in transition metal catalysis.[17-19] Ligands such as BINOL derived **17** are very useful in applications such as Rh-catalyzed hydrogenation of prochiral unsaturated substrates, or Cu-catalyzed conjugate additions of organometallic reagents to enones. By replacing the BINOL moiety with relatively inexpensive groups, such as biaryl bisphenols, comparable enantioselectivities have been achieved.[19]

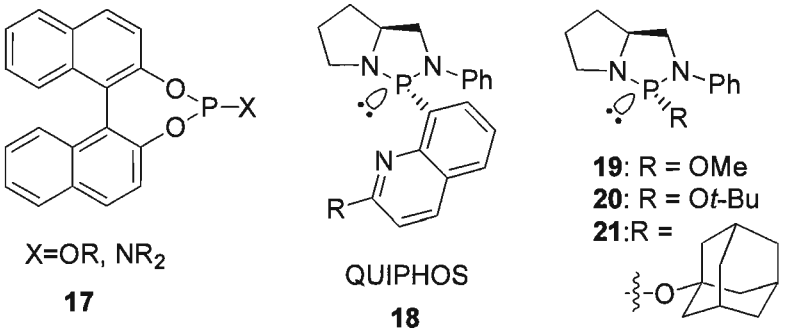
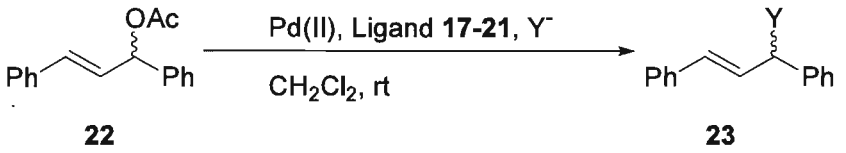


Figure 5. Examples of chiral phosphites and phosphorodiamidites[19]

In 2004, Tsarev and Lyubimov introduced a series of monodentate phosphorodiamidites with *P*-stereogenic atoms. According to early publications, such stereogenic centers led to good stereoselectivities in some transformations.[20] These chiral ligands contain pyrrolidine-dervied diamine backbones rather than the well-known BINOL moiety, and the reactivities of both the new system and the BINOL system were screened in Pd-catalyzed allylic substitution reactions of 1,3-diphenylallyl acetate **22** (**Scheme 3**).[19]



22 **23**

Scheme 3. Allylic substitution reaction with 1,3-diphenylallyl acetate[19]

Table 2. Results from Pd-catalyzed allylic substitution reactions of 1,3-diphenylallyl acetate (**22**) using **17-21**[19]

ligand	Y^-	Pd(II) source	yield (%)	ee (%) (*config*)
19	$NaSO_2pTol$	Pd(allyl)[a]	44	97 (*S*)
17	$NaSO_2pTol$	$Pd(allyl)Cl_2$	21	72 (*R*)
20	$PhCH_2NH_2$	$Pd(allyl)Cl_2$	76	95 (*R*)
17	$PhCH_2NH_2$	$Pd(allyl)Cl_2$	32	36 (*R*)
21	$CH_2(CO_2Me)_2$	$Pd(allyl)Cl_2$	98	97 (*S*)
17	$CH_2(CO_2Me)_2$	$Pd(allyl)Cl_2$	8	9 (*S*)
18	$CH_2(CO_2Me)_2$	$Pd(allyl)Cl_2$	--	85

[a] Generated in situ.

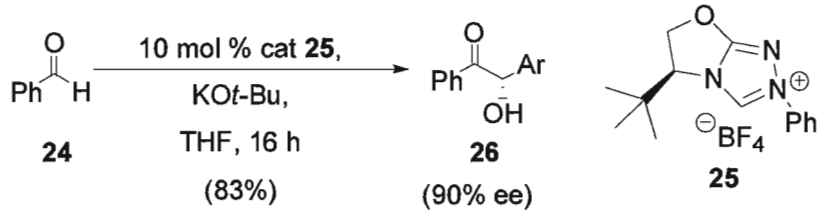
The results obtained indicate that catalysts **19-21** give higher enantioselectivities than BINOL derived ligands[21] by 12% ee. For allylic sulfonation, **19** gave 25% ee better selectivity than **17**. Ligand **20** gave 95% ee in allylic amination, but ligand **17** provided the same product in 36% ee. Finally, in allylic alkylation, **21** provided significantly higher yields than those obtained with **17** and QUIPHOS **18** (9% and 85% ee, respectively).[19]

1.2.c. N-Heterocyclic Carbenes (NHCs)

N-Heterocyclic carbenes (NHCs) are unusually stable single carbenes that are also sometimes insensitive to air.[22] They can be generated by deprotonation of azolium salts in THF. Since the mid-1990's, these compounds have been heavily investigated in asymmetric catalysis.[23,24] Significant reactions include the benzoin condensation and the Stetter reaction. Both of these reactions allow for the formation of a new carbon-carbon bond, with control of absolute stereochemistry.

The first enantioselectivity observed in the benzoin condensation was originally reported by Sheehan,[25] using a thiazolium catalyst in 1966. However, a low value of 26% optical purity was obtained. Over the years, increased selectivities were obtained in the benzoin condensation (**Scheme 4**). Particularly noteworthy are the triazolium salts that were prepared by Enders and Teles, which demonstrated exceptional selectivities (up to 99% ee).[26] These results were achieved by Enders in 2002 ultilizing a bicylic triazolium precatalyst **25**.[27] This catalyst generated adduct **26** from benzaldehyde in 90% ee employing a 10 mol% catalyst and KO*t*-Bu as base. Reducing the catalyst loading to 2.5

mol% led to a significant decrease in yield by 50%, but a slight improvement in enantiomeric excess (99% ee).[27, 28]



Scheme 4. Benzoin condensation catalyzed by **25**

Precatalysts **25** not only induced high enantioselectivities in the benzoin condensation, but was also employed in the Stetter reaction by Enders[27],[28] Rovis et al. manipulated the electronics of these catalysts and designed two families of new triazolium precursors, one of which is the pyrrolo-fused triazolium salt **28**, and the other of which is morpholine-derived **27**.[29,30]

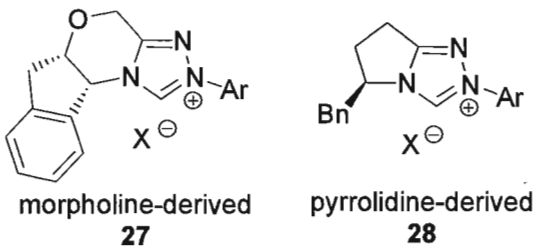
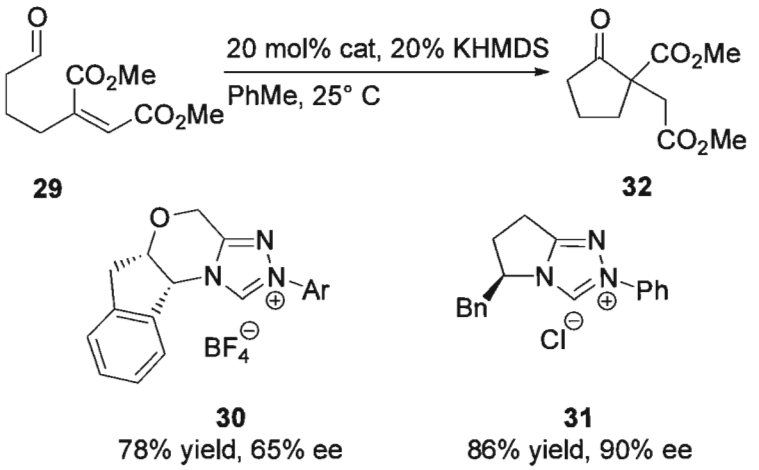


Figure 6. Triazolium precatalysts developed by Rovis et al.

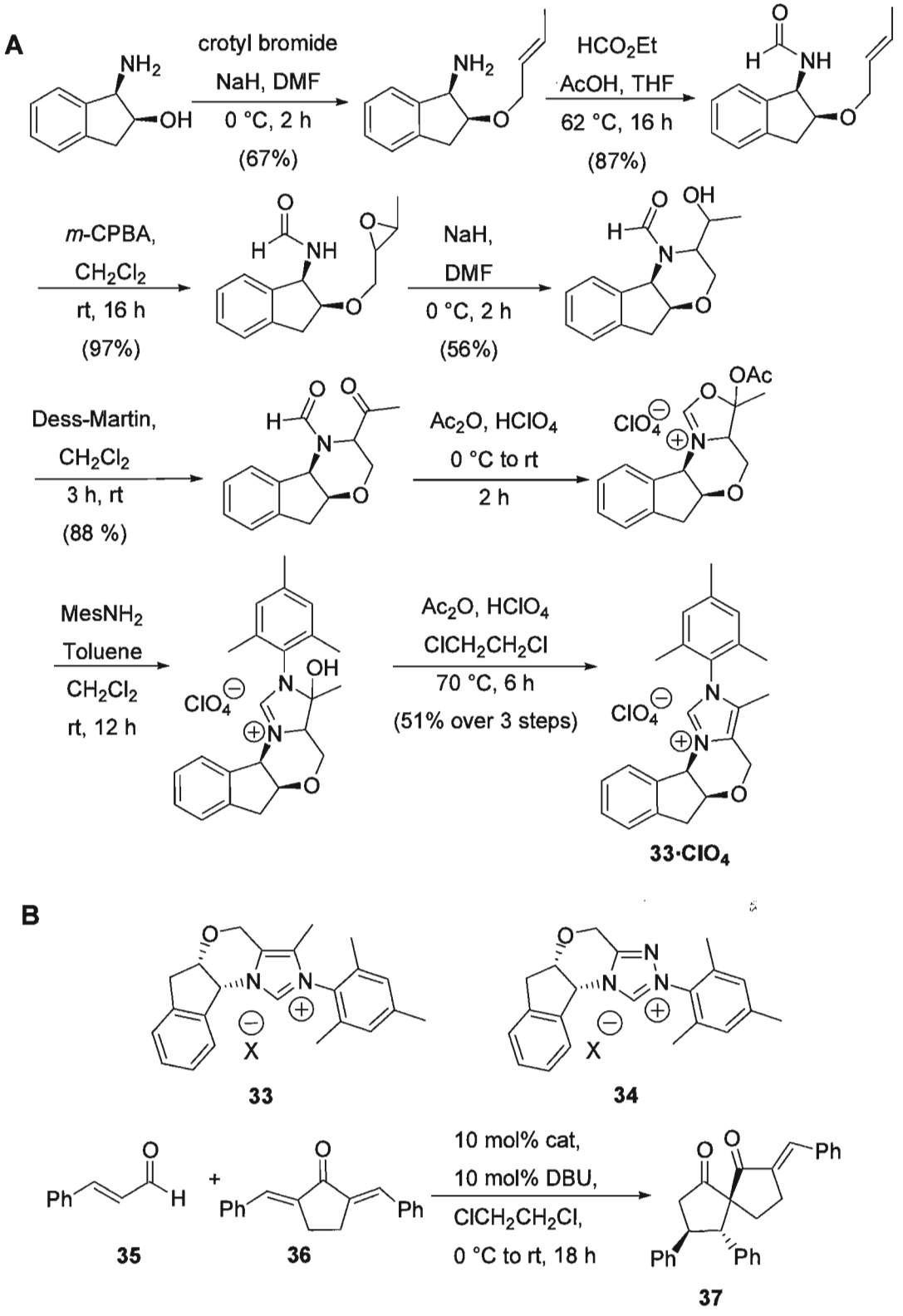
Following the applications of both precatalysts in several Stetter reactions, the morpholine derived precatalysts were shown to afford higher enantioselectivities than the pyrrolo-fused versions in most of the reactions.[29,31] However, the opposite trend was observed in the intramolecular cyclization of aliphatic aldehydes **29** (**Scheme 5**) to give

cyclopentanones **32**, for which **31** afforded the product in 90% ee versus 65% ee using **30**.[32]



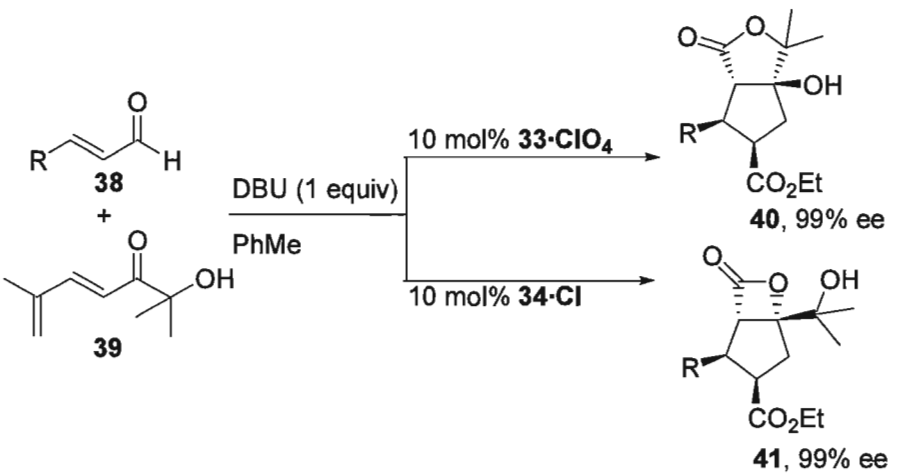
Scheme 5. Cyclization of **29** to **32**.[29,32]

On the other hand, Bode et al. noted earlier that there are few examples of highly enantioselective reaction catalyzed by chiral imidzolium-derived NHCs due to difficulties in their preparation. To draw a direct comparison of the reactivities of similar chiral triazolium and imidazolium precatalysts,[33] two almost identical reagents (**33** and **34**, **Scheme 6**) had to be synthesized. Notably, imidazolium **33** required an 8-step synthesis starting from a chiral *syn*-1,2-aminoalcohol.[34] Nonetheless, employment of precatalysts **33** and **34** in the formation of **37** resulted in better yield using **33** (34% versus 10%) but slightly lower enantioselectivity (85 versus 92% ee).[34]



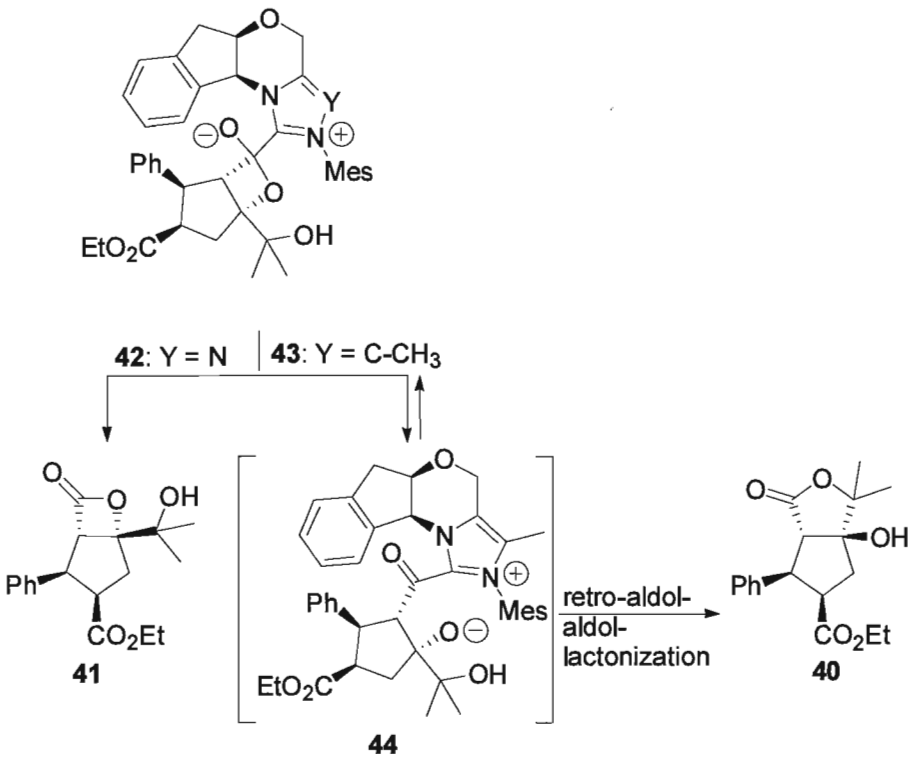
Scheme 6. A: Synthesis of **33·ClCO$_4$**; **B**: Spirocyclopentanone-forming annulation catalyzed by **35** and **36**[34]

In addition, precatalysts **33** and **34** led to products **40** or **41**, respectively; both were produced in 99% ee (**Scheme 7**).[35] The counter ion was shown to be important in these transformations in that the perchlorate of **33** was ideal for the formation of **40**, whereas the chloride salt of **34** was ideal for the formation of **41**.



Scheme 7. Enantioselective lactone synthesis using precatalysts **33** and **34**[35]

The difference in reactivity between otherwise identical imidazolium and triazolium-derived *N*-heterocyclic carbenes depends on the leaving group ability in acyl azolium species **42**, **43** involved in the lactone formation. Due to the nature of carbenes, it was postulated that the triazolium carbene is a better leaving group which provides the β-lactone **41** as the major product. However, in the case of the imidazolium species, elimination of alkoxide occurred in **44** which underwent a retro-aldol-aldol sequence to form the γ-lactone **40** (**Scheme 8**).[35]

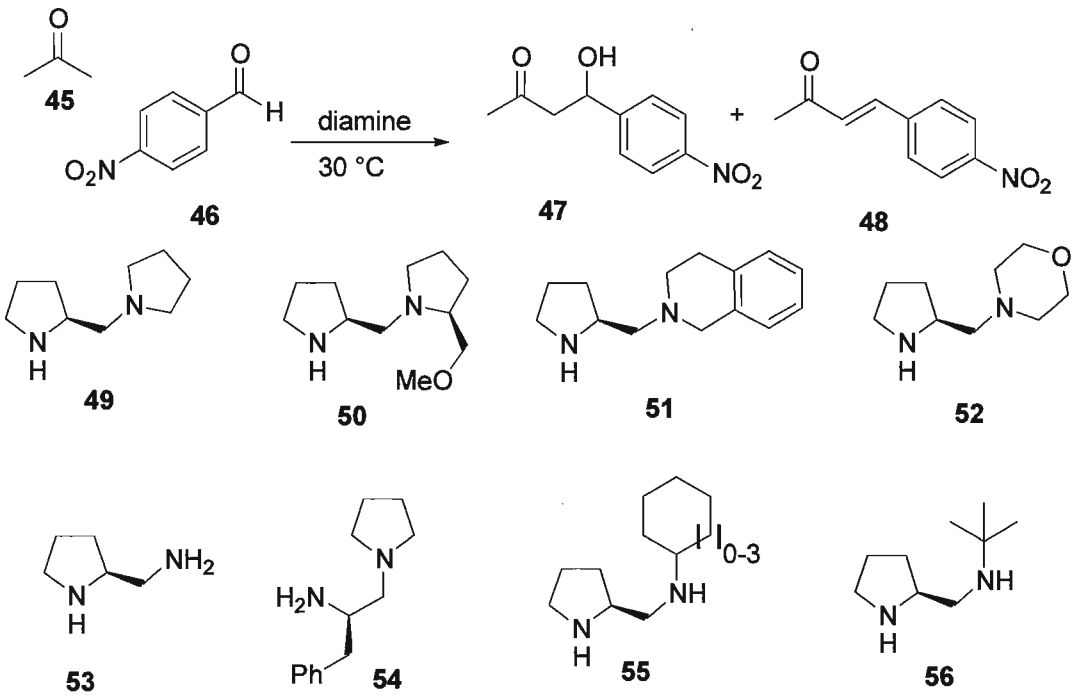


Scheme 8. The possible transformation of **42** to **40** and **41**[35]

This fascinating enantiodivergent reactivity between triazolium and imidazolium precatalyst encouraged us to design an alternate route to chiral imidazol(in)ylidene catalysts (vide infra).[36]

1.2.d. Proline-derived Diamines in the Aldol Reaction

Yamamoto et al has described the use of diamines **49-56** in the asymmetric direct aldol reaction.[37] These diamines contained a pyrrolidine backbone with chiral center(s). The selectivities produced from the aldol reaction between acetone and *p*-nitrobenzaldehyde varied according to diamine. The best results associated with these proline-derived diamines were obtained with TfOH salts of diamine **49**, which led to **47** in 60% yield and 88% ee.[38]



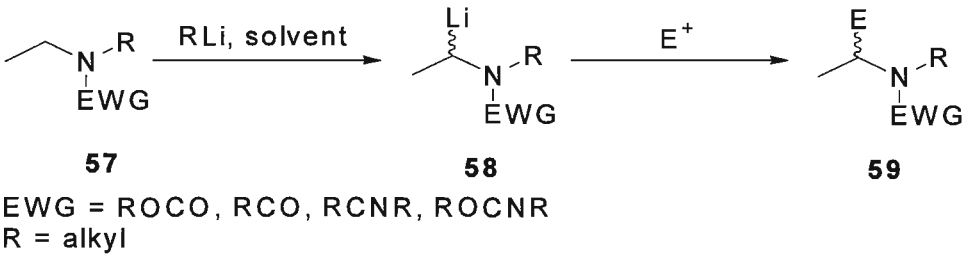
Scheme 9: Library of diamines screened for aldol reactions between acetone and 4-nitrobenzaldehyde[38]

1.3. Synthetic Approaches to Chiral Pyrrolidine Derivatives

The importance of the pyrrolidine functionality in natural products and catalysts has sparked the development of stereoselective synthetic methods to prepare these compounds. These methods involve the synthesis of pyrrolidine rings via cyclization of bis-homoallylic amines,[39] 1,3-dipolar cyclization,[40] reduction-cyclization of γ-aza ketones,[41] and Rh-catalyzed C-H insertion.[1] The method of choice, however, is asymmetric lithiation, which has been intensively investigated and extensively reviewed.[42] This approach is discussed below.

1.3.a. Asymmetric Lithiation-Substitution Alpha to Nitrogen

Asymmetric lithiation-substitution alpha to nitrogen was not considered to be feasible originally because it was thought that the alpha hydrogens were not acidic enough to be deprotonated, even with strong bases.[43] Yet, it was soon found to be feasible when nitrogen was activated with an electron withdrawing group, which simultaneously increased the acidity of the alpha protons while providing a place for the lithium base to coordinate to during lithiation (**Scheme 10**).[43] This finding initiated a new field of study with which to prepare chiral pyrrolidines, initially in racemic form, but later as single enantiomers.[42]



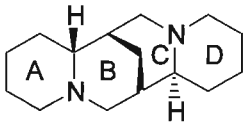
Scheme 10. An example of alpha to nitrogen lithiation-substitution

Thus, deprotonation of the carbon atom adjacent to the nitrogen, followed by electrophilic substitution not only provides a way to synthesize a functionalized amine - it also became an approach to prepare highly enantiomerically enriched products when homochiral diamine additives were employed to mediate the reaction (such as (–)-sparteine, **58**). This approach also allowed for control over regiochemistry. A related route involving lithiation of already chiral substrates has also been used. In the latter method, the lithiation-substitution process is diastereoselective rather than

enantioselective when chiral diamines are used. In general, organolithium compounds are important reagents in many synthetic organic transformations, and their applications have been extended to numerous asymmetric syntheses.[42]

1.3.b. (–)-Sparteine-Mediated Enantioselective Lithiation of Pyrrolidines

Isolated in large quantities by extraction of papilionaceous plants such as *Cytisus scoparius*, the commercially available (–)-sparteine (**58**) is a very well-known chiral diamine in used asymmetric synthesis.[44] This diamine has been explored as a ligand in asymmetric catalysis with various metals, such as the palladium-catalyzed Wacker cyclization to synthesize chiral dihydrobenzofurans, or the copper-mediated oxidative dearomatization of alkenyl benzaldehydes.[45]

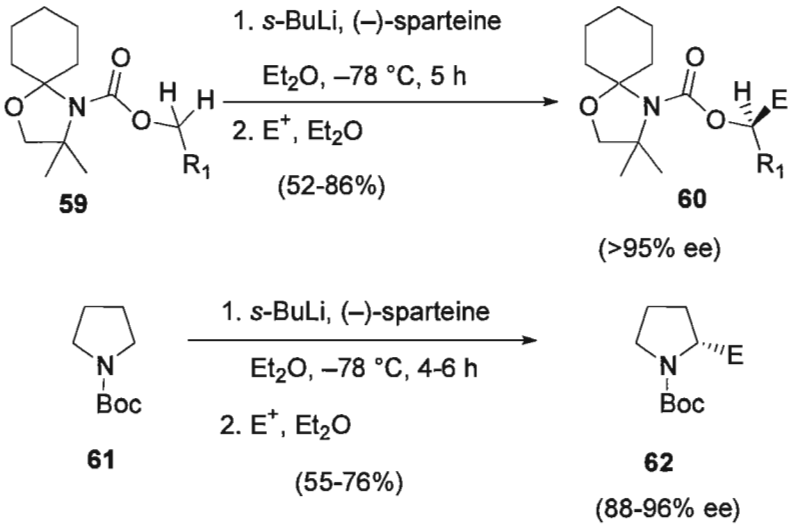


58

Figure 7. (–)-sparteine

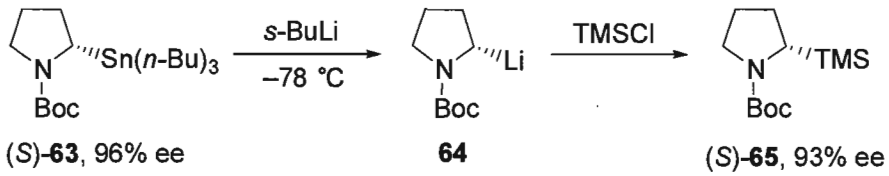
The first enantio-induction observed in a lithiation alpha to a heteroatom using (–)-sparteine was reported by Hoppe et al. in 1990, who employed *sec*-butyllithium (*s*-BuLi) to lithiate and α-oxyalkanides **59**, the result being that one of the two hydrogens next to the oxygen of the carbamate was preferentially removed. Following treatment with various electrophiles, this gave their desired products **60** in 52-86% yield and >95% ee.[46] This promising result inspired Beak et al. to apply the same approach using *N*-Boc

pyrrolidine **61** instead of α-oxyalkanides. This procedure afforded 2-substituted *N*-Boc pyrrolidines **62** in 55-76% yield and in 88-96% ee.[47,48] The electrophiles used by Beak et al. in this process were TMSCl (trimethylsilyl chloride), benzophenone, methyl iodide and tributyltin chloride (*n*-Bu_3SnCl).[49]



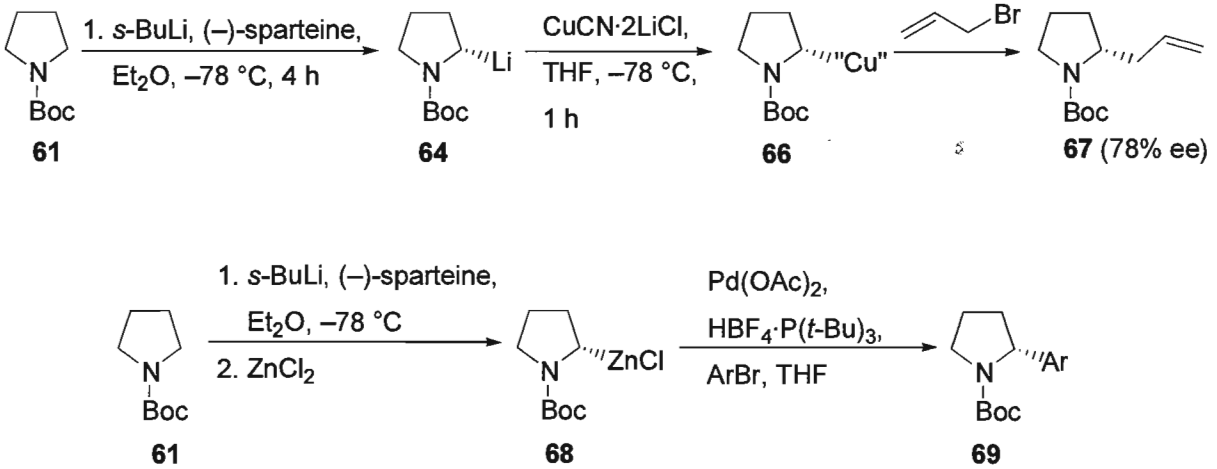
Scheme 11. The first examples of enantioselective lithiation alpha to heteroatoms using (–)-sparteine

Transmetalation from tin to lithium was used to confirm that the enantioselective step in this reaction occurred during deprotonation with the diamine/alkyllithium complex. In this respect, Beak subjected the enantioenriched stannane (*S*)-**63** (96% ee), to transmetalation and subsequently quenched with TMSCl to give (*S*)-**65**. The retention of stereochemistry after transmetalation clearly indicated that the deprotonation with *s*-BuLi and (–)-sparteine gave products with the same relative stereochemistry and that the enantiomer produced in the reaction was not affected by the nature of the electrophile. It also implied that carbanion **64** was configurationally stable.[49]



Scheme 12. Transmetalation from tin to lithium and subsequent electrophile quench

The intermediate carbanion generated in these asymmetric deprotonation can also undergo transmetalation with retention of chirality, allowing for the installation of a wide range of functional groups. In 2001, Dieter developed a method to introduce an allyl group next to the nitrogen atom in a series of substrates (including *N*-Boc pyrrolidine) with high enantioselectivities.[50, 51] The methods involved the use of copper(I) reagents for transmetalation after deprotonation with *s*-BuLi and before addition of allyl bromide (**Scheme 13**).

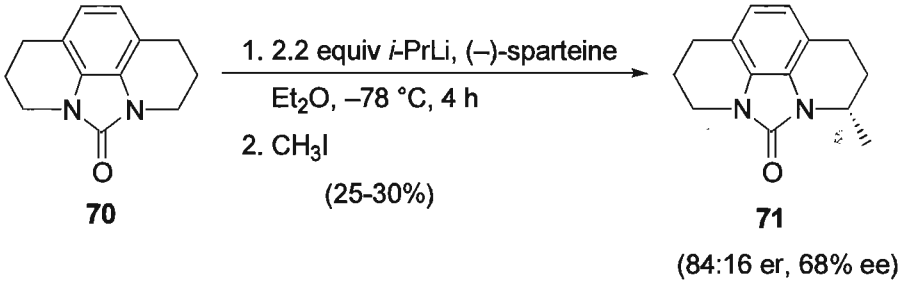


Scheme 13. Allylation of *N*-Boc pyrrolidine

Eventually, enantioselective palladium-catalyzed α-arylation of *N*-Boc-pyrrolidine carbanion was also reported to give enantiomerically enriched 2-arylpyrrolidines **69**. This

reaction proceeds by way of a zinc species, which then undergoes a Negishi cross-coupling with an aryl bromide, catalyzed by palladium acetate in combination with *t*-$Bu_3P{\cdot}HBF_4$. This method provided the arylated product in 92% ee and 72-82% yield **Scheme 13**.[52]

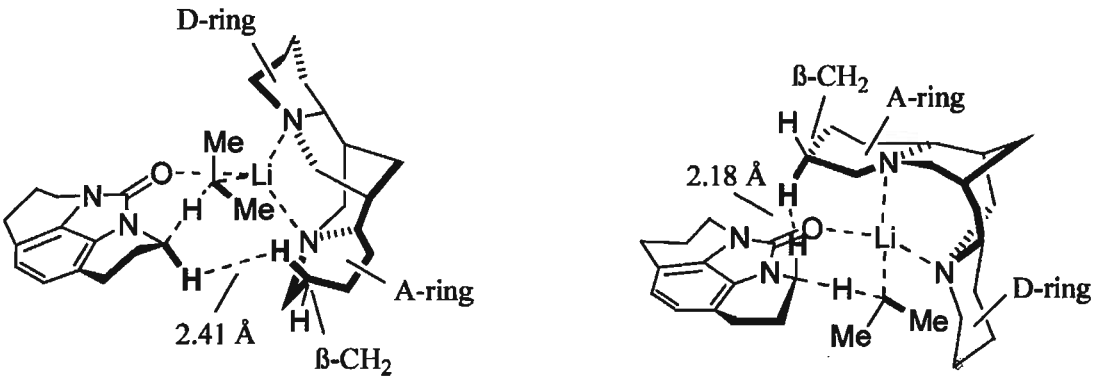
Other than *N*-Boc pyrrolidine, Metallinos and coworkers have reported that (–)-sparteine mediated asymmetric lithiation alpha to nitrogen is also feasible with urea-fused piperidines. Following a similar procedure, an octahydrophenanthroline-derived urea **70** was deprotonated and subsequently reacted with electrophiles to give **71** in low yield and moderate enantioselectivities (**Scheme 14**).[53] An in-depth transition state analysis for the deprotonation of urea **70** by the *i*-PrLi•(–)-sparteine complex was carried out at the MP2/6-316(d)//B3LYP/6-316(d) level of theory. The result indicated the removal of the equatorial pro-*S* hydrogen is favoured over the axial proton, which follows into the trend observed in **61** and *N*-Boc-piperidine.[54, 55]



Scheme 14. Lithiation of piperidyl-fused urea **70**

The transition states (TS) for both pro-*R* and pro-*S* hydrogen removal showed that the A-ring of (–)-sparteine is directly on top of the site of proton transfer (**Figure 8**). Interactions between a β-CH_2-hydrogen in the A-ring of (–)-sparteine and the axial-hydrogen of **70** alpha to nitrogen *not undergoing deprotonation* controlled the

stereochemistry of the reaction.[53] As shown in **Figure 8**, the H···H distance between the β-CH_2 in the A ring and the axial hydrogen of the α-carbon in **TS2** is 2.18 Å. This close contact leads to destabilization in **TS2**. On the other hand, the H···H distance in **TS1** is 2.41 Å, which is close to the sum of the van der Waals radii of two hydrogen atoms. The $\Delta\Delta E$ value calculated from quantum chemical transition state study was 1.26 kcal/mol, implying an enantiomeric ratio (er) 89:11 favoring the pro-*S* equatorial proton removal, which is in agreement with the experimental results. The predicted stereochemistry of the reaction was confirmed by crystallographic analysis. This computational analysis also provided an explanation for why the A-ring of (–)-sparteine is so important for obtaining high levels of enantioinduction.[54, 55]

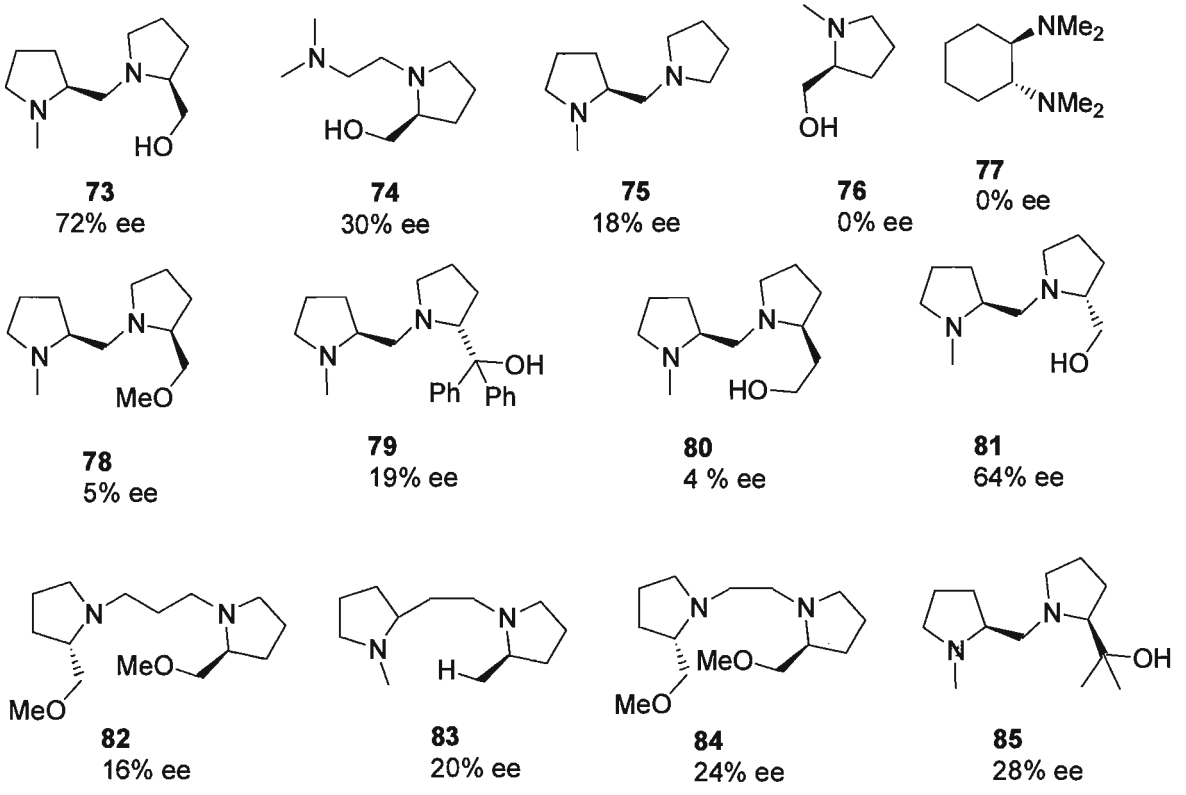


TS1 (pro-*S*) **TS2** (pro-*R*)

Figure 8. Transition states for pro-*S*-**72** and pro-*R*-**72** lithiation[53]

Although (–)-sparteine has generated highly enantioenriched products in asymmetric lithiation, there are difficulties in producing opposite enantiomers in these reactions due to the lack (+)-sparteine. Unlike its enantiomer, (+)-sparteine is only available in small quantities from nature or through synthetic preparation.[56]

In 1995, the Beak group published the results of roughly 20 chiral ligands **73-85** used in asymmetric deprotonation of *N*-Boc pyrrolidine **61** in which all reactions were quenched with TMSCl.[54] However, none of these chiral ligands produced comparable results as that of (–)-sparteine.[54] Based on these findings, O'Brien and co-workers initiated a research focus on the synthesis of diamines that would behave as (+)-sparteine surrogates.[56]



73 72% ee
74 30% ee
75 18% ee
76 0% ee
77 0% ee
78 5% ee
79 19% ee
80 4 % ee
81 64% ee
82 16% ee
83 20% ee
84 24% ee
85 28% ee

Figure 9. Structures of the diamines studied by Beak et al.[57]

From Beak's Chem3D space-filling diagrams (**Figure 10**) of a hypothetical (–)-sparteine/Li[54] complex, the D ring of (–)-sparteine appeared to be turned away from the "business end"[56] of the complex. In their design process, O'Brien and co-workers removed the D-ring, and added a methyl group to that nitrogen, giving an "*N*-methyl (+)-

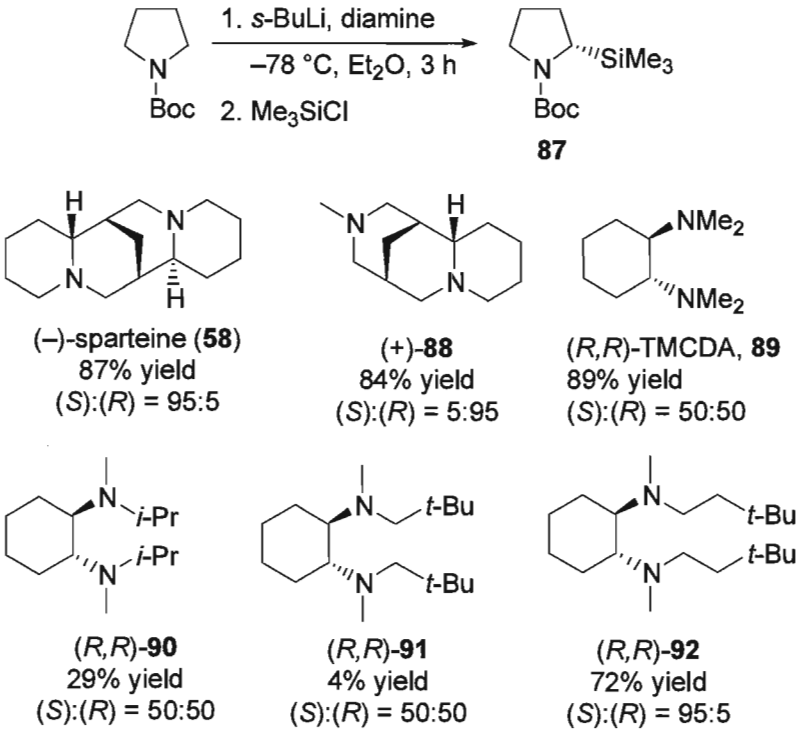
sparteine surrogate". It has been shown that the "*N*-methyl (+)-sparteine surrogate" gives similar but opposite enantioselectivities in the kinetically controlled asymmetric deprotonation reactions; however, it gives poor selectivity when used in dynamic thermodynamic reactions as compared to (–)-sparteine.

A B

86

Figure 10. Chem3D model of (–)-sparteine[44]

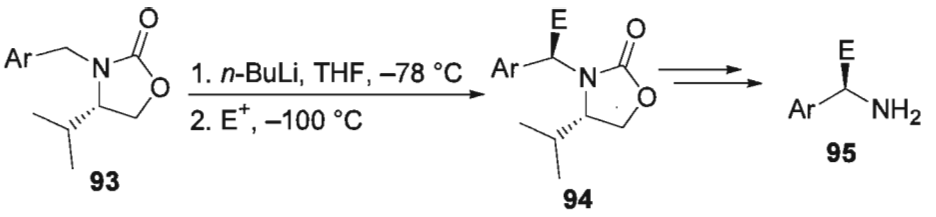
Alternative (+)-sparteine surrogates are chiral cyclohexyl diamines (**89-92, Scheme 15**) which were first synthesized by Alexakis' group[58,59] and were employed in asymmetric syntheses by Bailey[55,60]. These diamines were subsequently tested by both Alexakis and O'Brien for their selectivity and reactivity compared to (–)-sparteine in various organolithium reactions.[61] In a series of 2008 publications, O'Brien explored these diamines in an asymmetric deprotonation of *N*-Boc pyrrolidine. The results obtained for silyl adduct **87** were comparable to what would be expected with (+)-sparteine. These diamines may be produced easily in both enantiomeric forms, thus allowing the production of the both enantiomers of **87** in high ee.[61,62,63]



Scheme 15. Screening of chiral diamines in *N*-Boc pyrrolidine lithiation

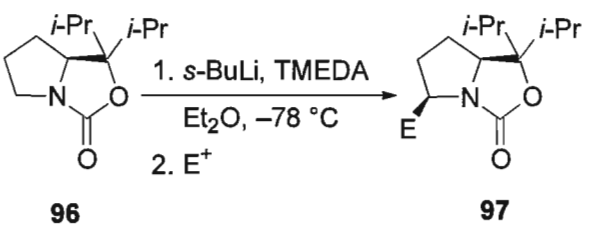
1.3.c. Diastereoselective Lithiation alpha to Nitrogen

Asymmetric synthesis of primary benzyl amines **95** via oxazolidinone derived organolithium intermediates was developed by Gawley, giving good yields and excellent diastereoselectivities (**Scheme 16**). The alkylated products (**94**) were hydrolyzed, followed by oxidative cleavage of the amino alcohol to generate chiral primary amines in high enantiomeric purity.[64]

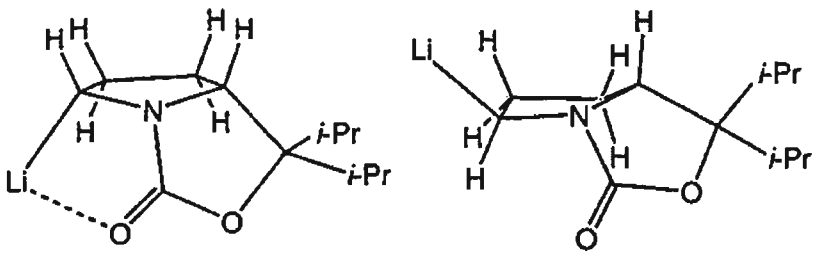


Scheme 16. Synthesis of chiral benzylamines from oxazolidones via diastereoselective lithiation

In the case of a bicyclic carbamates or oxozolidones **96**, Beak reported that these reactions undergo diastereoselective lithiation without the use of chiral diamines owing to the presence of a chiral center in the substrate to give products **97** with *syn* stereochemistry.[65] It was explained that removal of one of the pro-*S* protons is favoured and the resulting anion is highly configurationally stable. Computational calculations, carried out at the PM3 level, showed that the pro-*S* proton had a much shorter distance to the carbonyl oxygen (2.78 Å) than the pro-*R* proton (3.70 Å, **Figure 11**), which kinetically favoured lithiation by virtue of proximity of the coordinated alkyllithium to the carbonyl oxygen.



Scheme 17. Diastereoselective lithiation of **96**



syn-**98** *anti*-**98**

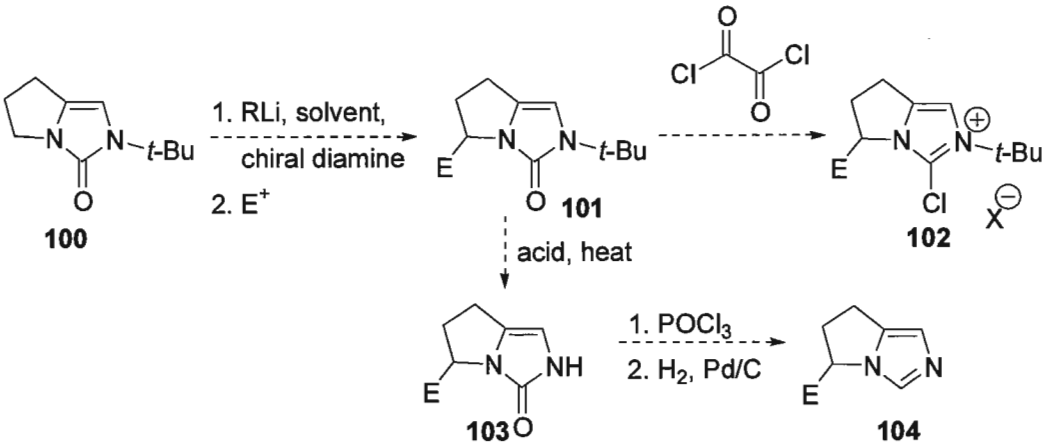
Figure 11. Cartoon of *syn* versus *anti*-**98** carbanions; Calculations were carried out at the PM3 level of theory [65]

1.5. Aims and Objectives:

The lack of convenient access to enantio- or diastereomerically enriched pyrroloimidazole derivatives with biological activity, as well as the paucity of annulated chiral imidazol(in)ium precatalysts,[66] prompted us to explore a viable synthetic routes to prepare both of these targets by using asymmetric lithiation of urea **70**, using reactions of *N*-Boc pyrrolidine **61** and cyclic carbamate **96** as precedent. Two different urea starting materials, one saturated (chiral) and one unsaturated (achiral), will be prepared to test this approach.

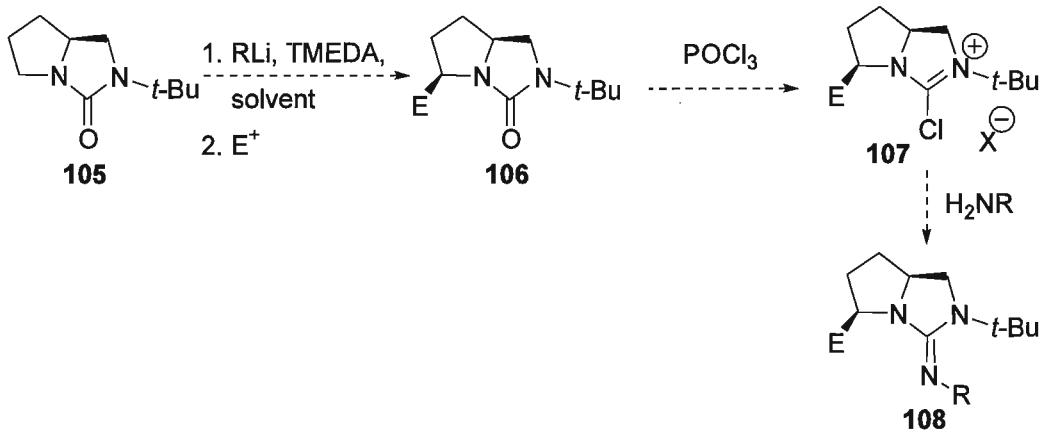
To begin our investigation, unsaturated urea **100** (**Scheme 17**) will be subjected to various conditions, such as different chiral diamines, solvents and alkyllithiums to determine the best conditions for enantioselective lithiation. With best conditions determined, the scope of the process will be evaluated by using different electrophiles to produce variously alpha-substituted products **101**. The enantio-enriched **101** will ideally undergo dealkylation of the *t*-butyl group under acidic conditions to give **103**, and

functional group manipulation (oxalyl chloride or $POCl_3$ and then reduction) will afford the target biologically active compounds **104**. Alternatively, direct treatment of **101** with $POCl_3$ will give direct access to chiral annulated imidazolium salts **102**, which may serve as immediate precursors to NHCs by chlorine-lithium exchange at low temperature.



Scheme 18a. Proposed routes to synthetic targets **102** and **104**.

The chiral saturated urea congener **105** will also be synthesized and subjected to similar lithiation-substitution to give diastereomerically pure products **106**, which may be converted to as imidazolinium precatalysts **107** or trapped with primary amines in situ to give guanidine catalysts **108**.

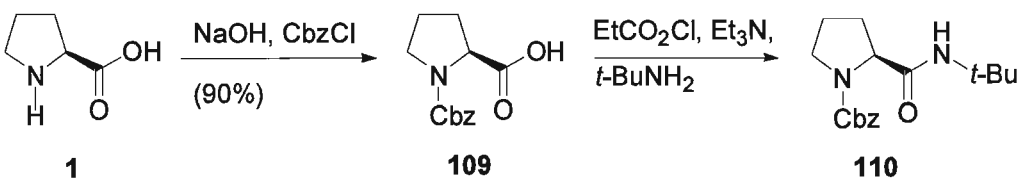


Scheme 18b. Proposed route to chiral annulated imidazolinium salts **107** and guanidines **108**

2. Results and Discussion:

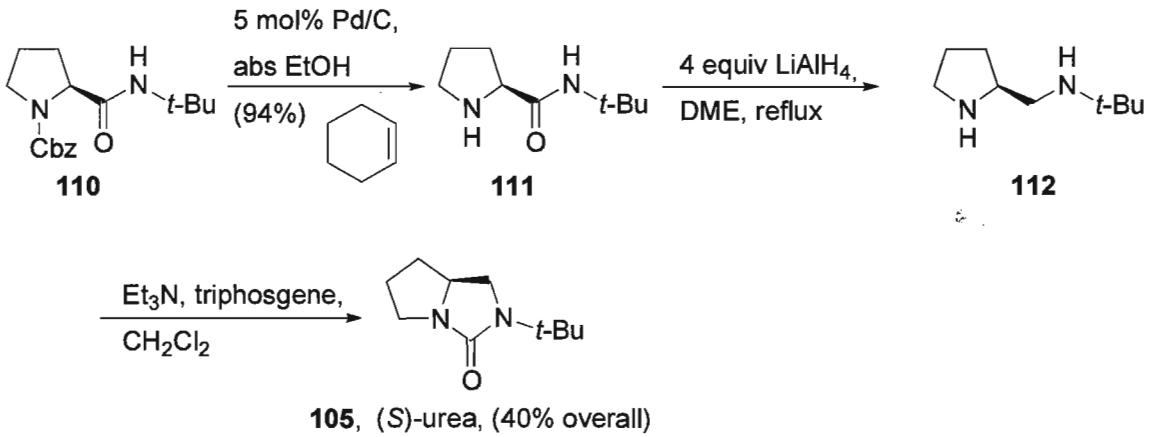
2.1. Preparation of 2-*tert*-Butyl-hexahydropyrrolo[1,2-c]imidazol-3-one (105) and 2-*tert*-Butyl-2,5,6,7-tetrahydropyrrolo[1,2-c]imidazol-3-one (100)

To begin our investigations, both ureas **100** and **105** needed to be readily prepared, ideally from a common starting material (**Scheme 19**).[36] Compound **110** [67] was identified as a common precursor to both ureas. Following reported procedures, L-proline **1** was protected with CbzCl (benzyl chloroformate) to give carboxylic acid **109**, which was converted to the *t*-Bu amide **110** via activation with ethyl chloroformate and addition of *t*-butylamine. The overall yield for this process was 81%.



Scheme 19. Preparation of **110**

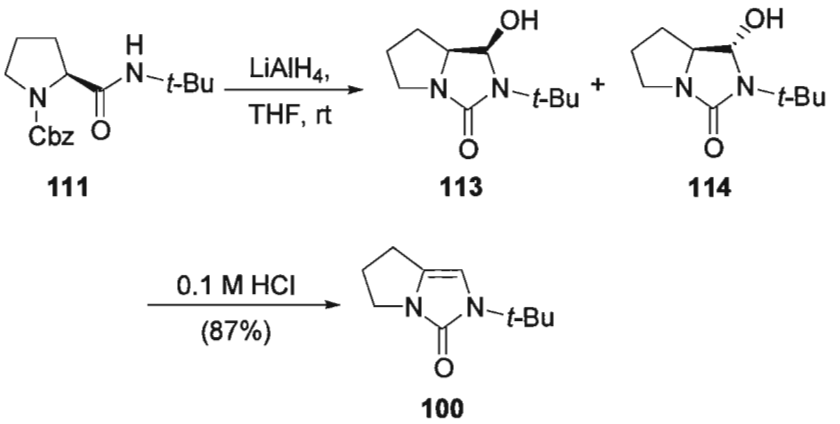
Amide **110** was deprotected under standard conditions using cyclohexene and palladium on carbon (Pd/C) in ethanol to give amine **111** (**Scheme 20**). Attempts to reduce the *tert*-butyl amide in **111** with lithium aluminum hydride ($LiAlH_4$)[11] in refluxing tetrahydrofuran (THF) were unsuccessful, even after 16 hours. However, changing the solvent to 1,2-dimethoxyethane (DME) allowed for full consumption of the starting material **111** to give diamine **112**. The volatility of diamine **112** made it necessary to convert it directly to urea **105** by treatment with triphosgene and triethylamine in dichloromethane (CH_2Cl_2) solvent. This procedure afforded urea **105** in 40% overall yield as a colorless oil. That urea **105** was still enantiomerically pure after this sequence of reactions was confirmed by chiral HPLC analysis where the minor enantiomer was completely undetectable.



Scheme 20. Synthesis of **105**

The synthesis of the unsaturated urea, 2-*tert*-butyl-2,5,6,7-tetrahydro-pyrrolo[1,2-c]imidazol-3-one **100** (**Scheme 21**), followed a similar procedure as for 2-*iso*-propyl-2,5,6,7-tetrahydro-pyrrolo[1,2-c]imidazol-3-one **118** reported by Kiyooka[68] in 1981

(**Scheme 22**). The procedure involved treatment of **45** with $LiAlH_4$ in THF at room temperature, this allowed cyclization to form a new ring. Unlike Kiyooka's system, the alcohol **113** and **114** were isolable. This mixture of hemiaminals could be treated with dilute acid to provide the desired product, 2-*tert*-butyl-2,5,6,7-tetrahydro-pyrrolo[1,2-c]imidazol-3-one **100** in good yield.



Scheme 21. Preparation of **100**

Amino alcohol **113** can be isolated as a single diastereomer through crystallization in ethyl acetate (EtOAc). To determine the stereochemistry of this compound, nuclear Overhauser effect (NOE) difference spectroscopy was performed in acetone-d_6. As shown in the 1D-NOE spectrum of **113** (**Figure 12**), irradiating H_B (red proton, upside-down signal at 5.35-5.33 ppm), enhanced the H_A signal (blue proton, upright signal at 3.81 ppm). This result inferred that these two protons were on the same face of the molecule, indicating *syn* stereochemistry.

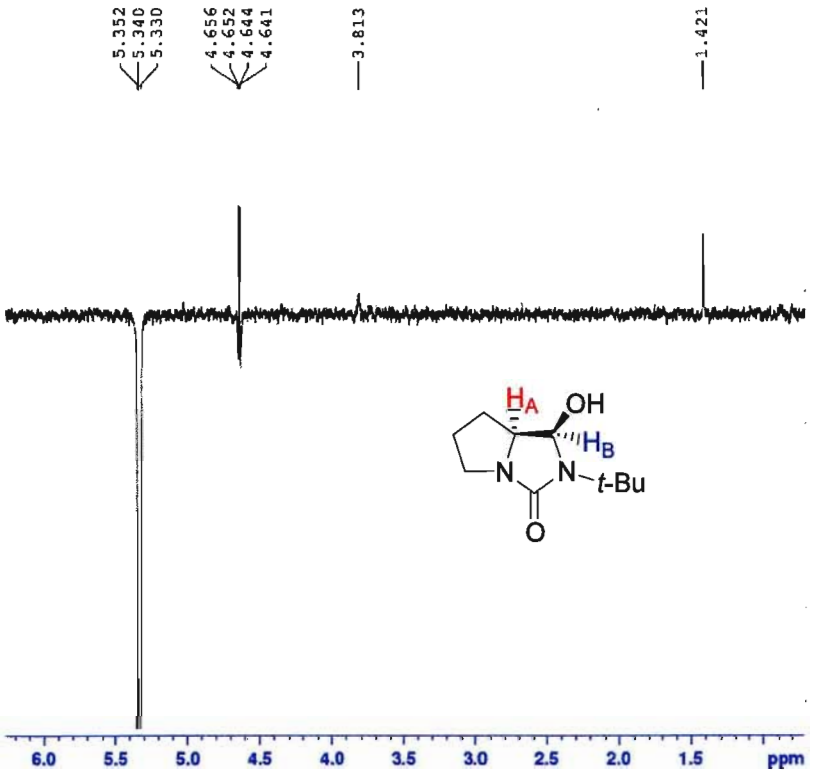
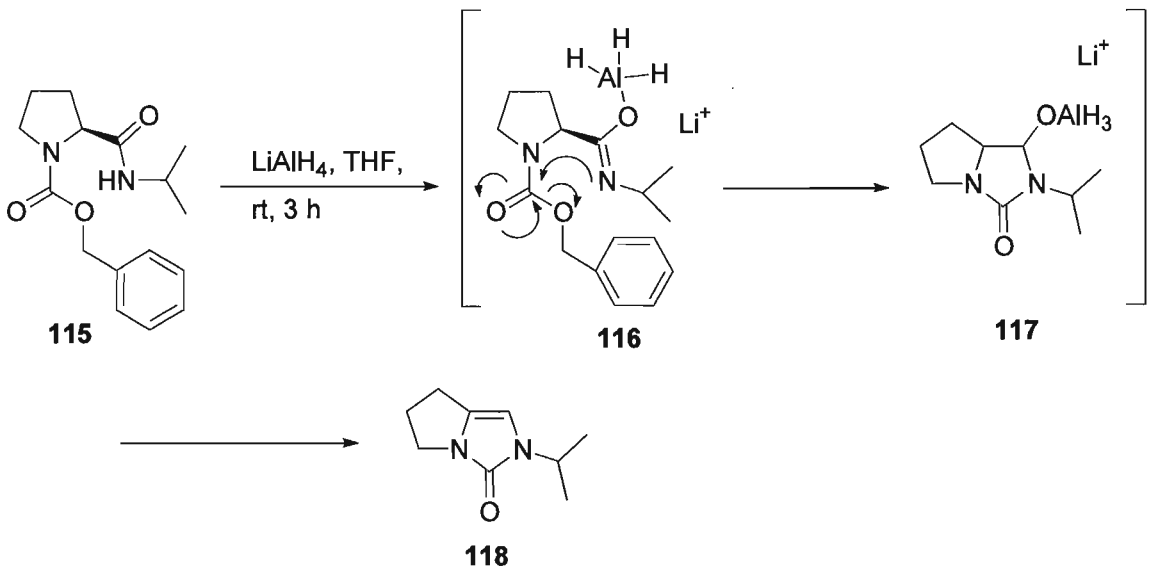


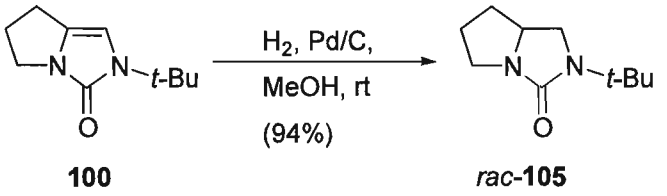
Figure 12. Selective irradiation difference NOE spectrum for **113**

A possible mechanism for the cyclization of Cbz-L-proline compound **111** was described in Kiyooka's paper.[68] In their studies of solvent effects in the reaction of (*S*)-*N*-isopropyl-*N*-benzyloxyl carbonyl) prolinamide **115** with $LiAlH_4$, they discovered that only THF at room temperature would lead to **116**. Using diethyl ether solvent normally reduced the Cbz group. It was proposed that the substrate underwent an elimination from intermediate **117** to give the unsaturated urea (**118**, **Scheme 22**), unlike in **113/114** which were isolable.



Scheme 22. Kiyooka proposed mechanism for cyclization to **118**[68]

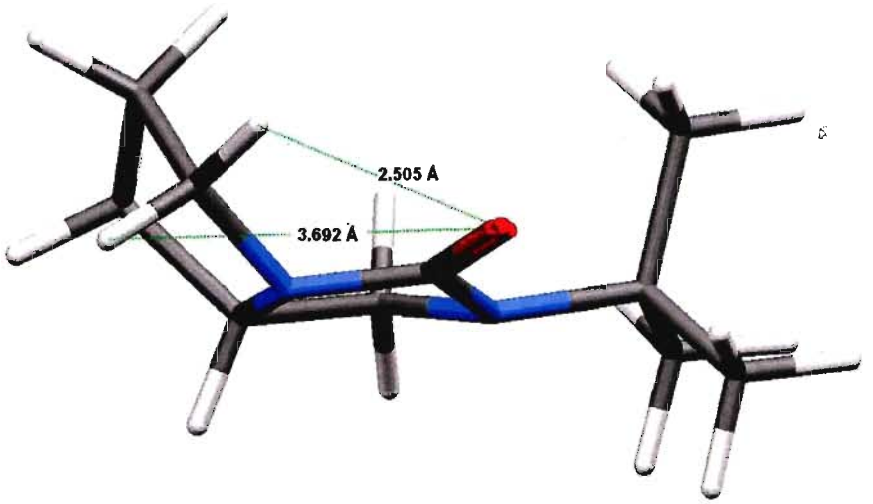
Hydrogenation of **100** provided access to the racemic version of **105**, which ensured a simple way of preparing racemic alpha substituted congeners for eventual enantiomeric purity determinations of products by chiral HPLC analysis (vide infra). Thus, subjecting **100** to Pd/C in ethanol under one atmosphere of hydrogen for 18 hours yielded the *rac*-**105** in 94% yield.[36]



Scheme 23. Hydrogenation of **100** to *rac*-**105**

2.2. Diastereoselective Lithiation of 2-*tert*-Butyl-hexahydro-pyrrolo[1,2-c]imidazol-3-one 105.

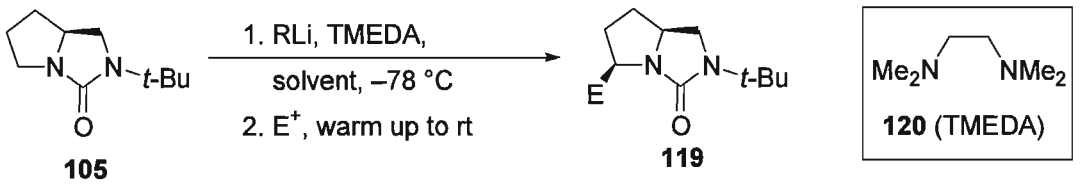
A computational minimization was carried out on **105** [B3LYP/6-31G(d)] to determine the distances between the urea oxygen atom and the pro-*S* and pro-*R* alpha methylene hydrogens.[36] A large difference in distance would indicate preferential lithiation of one hydrogen atom over the other because the alkyllithium base would be in closer proximity to one hydrogen upon coordination to oxygen. As shown in the **Figure 13** below, the distances between the urea oxygen and the pro-*S* proton was 2.505 Å compared to 3.692 Å for the pro-*R* proton, a difference of 1.187 Å. Since the difference in distance between the carbonyl oxygen and the pro-*R* and pro-*S* alpha hydrogens in carbamate **96** (**Scheme 17**) was calculated by Beak to be 0.92 Å, this result indicates that alpha lithiation of **105** should be at least as diastereoselective as **96**.[69,36]



105

Figure 13. Minimized structure of **105**[70] [B3LYP/6-31G(d)]; red = oxygen, blue = nitrogen, white = hydrogen, grey = carbon.

Lithiation of 2-*tert*-butyl-hexahydro-pyrrolo[1,2-c]imidazol-3-one **105** was carried out at –78 °C, the same temperature that was used for *N*-Boc pyrrolidine. Several reactions were performed to determine the most suitable solvent and alkyllithium for this transformation.



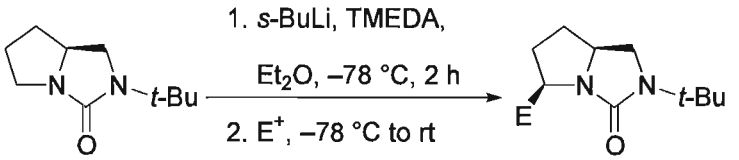
Scheme 24. Diastereoselective lithiation **105**

THF and diethyl ether (Et_2O) were used as solvents to establish the better medium for this particular reaction. The reaction mixture was treated with tetramethylethylenediamine (**120**, TMEDA) and *s*-BuLi at kept at –78 °C for two hours. After this time, trimethylsilyl chloride (TMSCl), trimethystannyl chloride ($SnMe_3Cl$) or deuterated methanol (MeOD) was added and the product yields determined. As seen in **Table 3**, significantly better yields were obtained when the reaction was carrried out in diethyl ether, and so this solvent was chosen for subsequent experiments.

Table 3. Lithiation of **105** with *s*-BuLi/TMEDA in THF or Et_2O

E^+	E	yield (%) in THF	yield (%) in Et_2O,
TMSCl	TMS	15	63
$SnMe_3Cl$	$SnMe_3$	53	55
MeOD	D	17	32

The remaining lithiation-substitution reactions were performed in Et_2O with TMEDA and *s*-BuLi. The putative alpha carbanion was then trapped with either benzophenone, Me_2SO_4, TMSCl, $SnMe_3Cl$ or CO_2 (from dry ice sublimation). Yields from these reactions ranged from 55% to 80%. All of the preceding products were obtained as single diastereomers, as determined by ^1H and ^{13}C NMR analysis. The *syn* relative stereochemistry was determined by NOE spectroscopy (vide infra).[36]



105 **121-126**

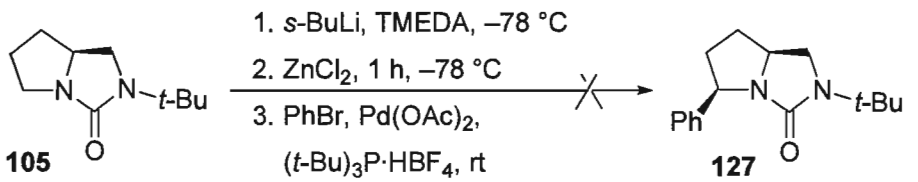
Scheme 25. Diastereoselective lithiation-electrophile quench of **105** in Et_2O

Table 4. Electrophiles employed in the diastereoselective lithiation of **105**

E^+	E	Product	yield, %
Ph_2CO	Ph_2COH	**121**	60
Me_2SO_4	Me	**122**	55
allyl bromide[a]	allyl	**123**	50
$SiMe_3Cl$	$SiMe_3$	**124**	63
$SnMe_3Cl$	$SnMe_3$	**125**	55
CO_2	CO_2H	**126**	80

[a] via CuCN·2LiCl transmetalation.

For slower reacting electrophiles such as allyl bromide, Dieter has shown that transmetalation to the copper species preserves stereochemical integrity of the carbanion.[50] Thus, transmetalation of the alpha lithio intermediate with CuCN·2LiCl before addition of allyl bromide gave **123** in 50% yield, again as a single diastereomer. It is worth mentioning that omitting the copper (I) transmetalation step for the electrophile benzyl bromide resulted in formation of a diastereomeric mixture of benzylated products in low yield (this result was not included in the thesis for lack of complete characterization of the products). On a related note, an attempt to perform a Negishi coupling to produce arylated product **127** was unsuccessful at room temperature after transmetalation with $ZnCl_2$.



Scheme 26. Attempted arylation of **105**

To determine the stereochemistry of the preceding products, NOESY or difference NOE experiments were carried out. For the benzophenone adduct, a Heteronuclear Single Quantum Coherence (HSQC) NMR experiment was carried out to identify the proton-carbon connectivities. The methine protons of interested were at 4.25 ppm and 3.73 ppm (**Figure 14**).

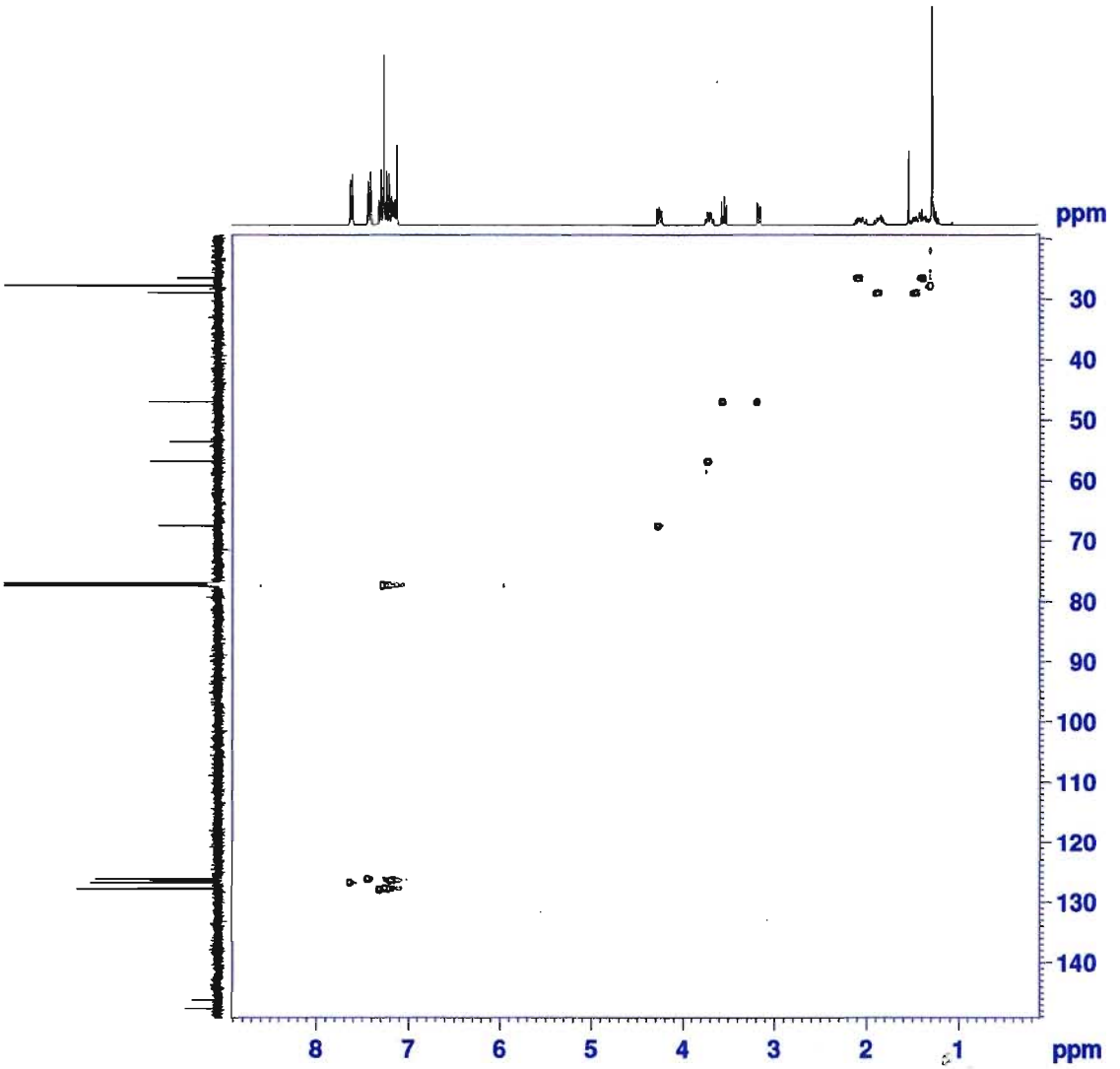


Figure 14. HSQC spectrum of **121**

In the NOESY spectrum of **121**, a correlation cross peak between these same methine protons (green and blue) were observed (**Figure 15**). This result suggested that the two protons were on the same side of the molecule, which supported the *syn* stereochemistry of the products. This result coincides with Beak's observation on cyclic carbamate **96**.

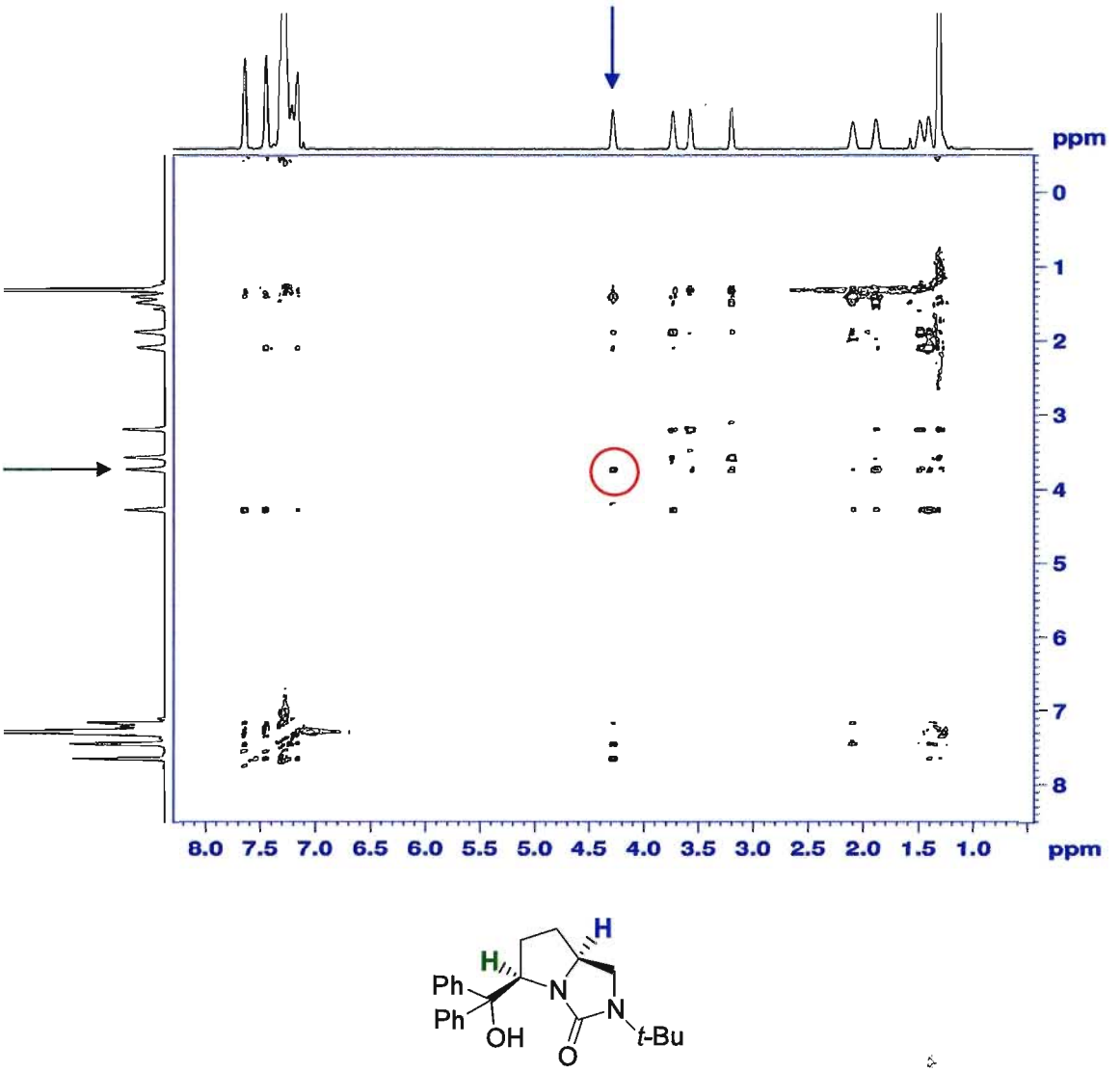


Figure 15. NOESY spectrum of **121**

To confirm the *syn* stereochemistry of the other products, 1D-NOE spectroscopy was carried out for **122**, **123** and **125**. In all three cases, experiments clearly showed that the methine protons of interest were on the same face of the molecule, as in **121**. For example, in the 1D-NOE of **122**, irradiation of a proton from the pyrrolidine methylene groups at 2.1 and 1.9 ppm led to enhancements of the key methine protons at 3.8 and 3.6 ppm. Similar enhancements were observed in the 1-D NOE spectra of **123** and **125**.

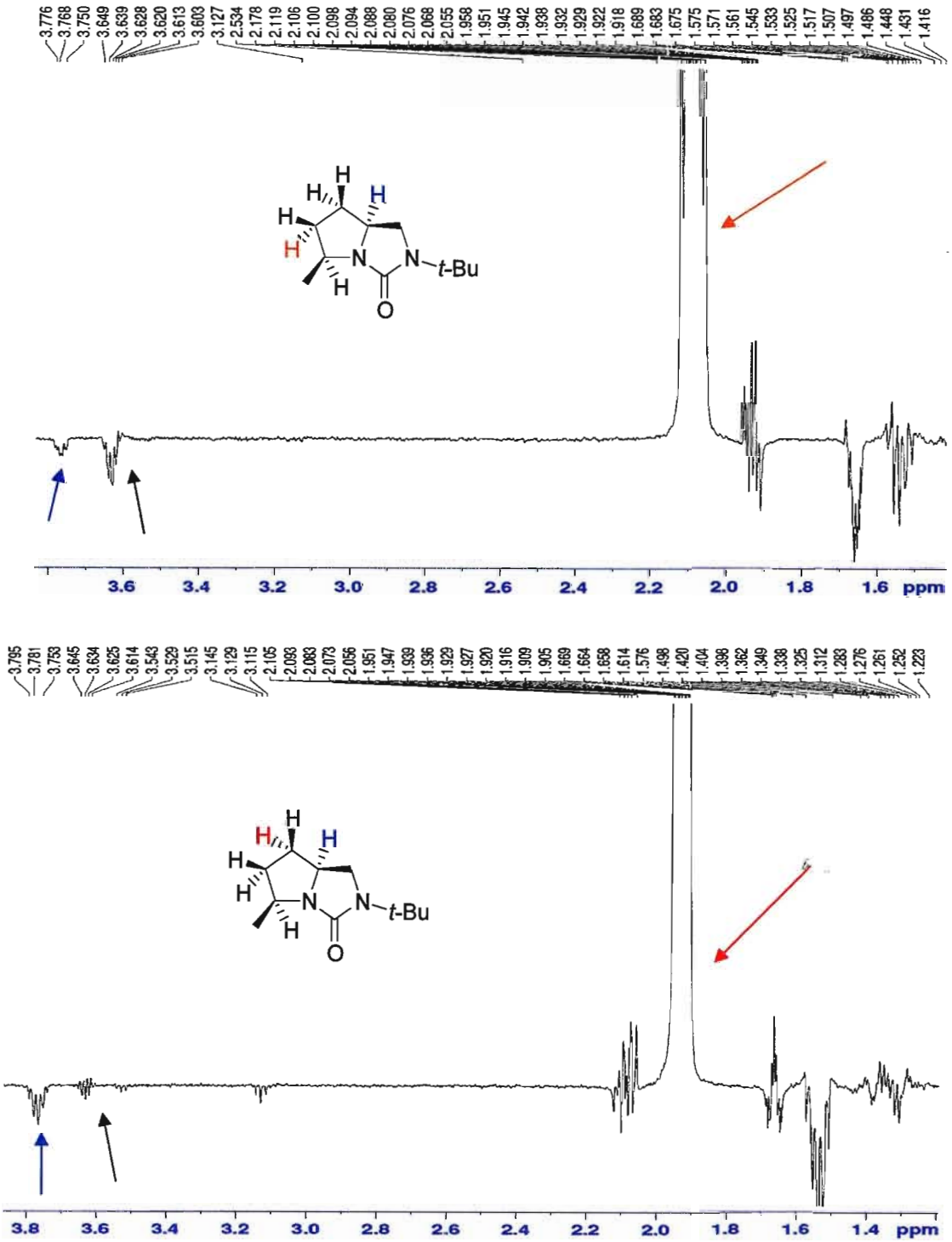
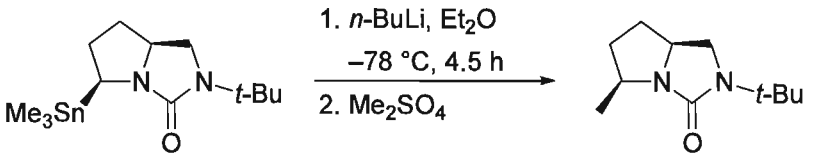


Figure 16. 1-D NOE selective irradiation experiments of *syn*-**122**

The *syn* stereochemistry of **125** was further confirmed by transmetalation of tin with *n*-BuLi at low temperature, which after 4.5 h was treated with Me_2SO_4 to give exclusively *syn*-**122**. This experiment also showed that the alpha-lithio intermediate is configurationally stable for prolonged periods at low temperatures.

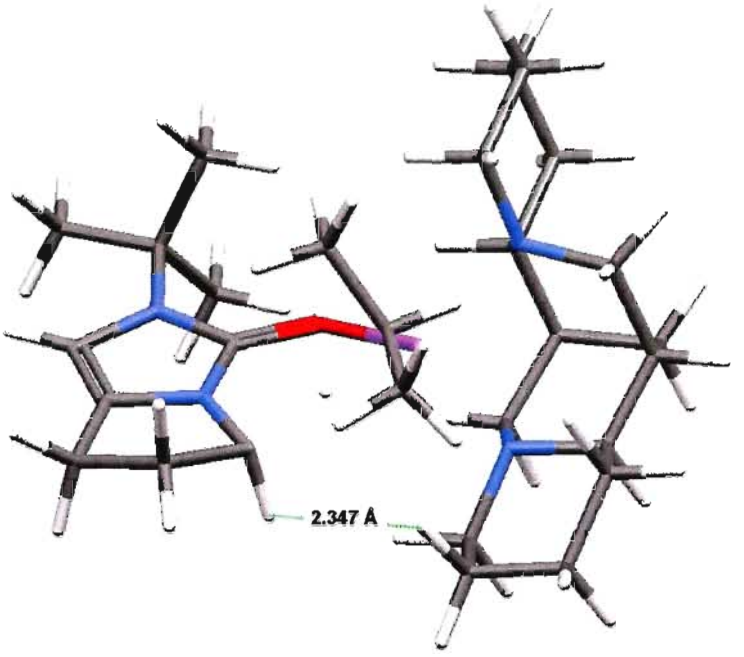


125 (–)-*syn*-**122**

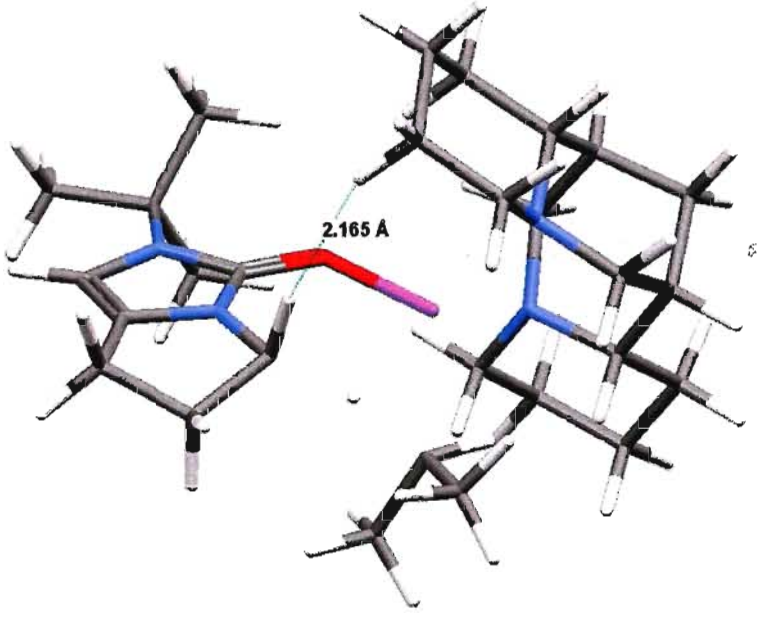
Scheme 27: Transmetalation of **125** to *syn*-**122**

2.3. Enantioselective Lithiation-Substitution of 2-*tert*-Butyl-2,5,6,7-tetrahydro-pyrrolo[1,2-c]imidazol-3-one 100

Following the example of phenanthroline-derived urea **70**, computational calculations of the transition states of lithiation of unsaturated urea **100** with **58**·*i*-PrLi complex were carried out at the MP2/6-316(d)//B3LYP/6-316(d) level. In transition state 1 (**TS1**, pro-*S*), the axial proton of **100** was calculated to be 2.347 Å away from the β-CH_2 of **58**. In contrast, **TS2** (pro-*R* lithiation) gave an analogous H···H contact distance of only 2.165 Å, indicating a disfavored and destabilized transition state. Energetically, ΔΔE for **TS1** and **TS2** was found to be 1.68 kcal/mol, which corresponds to a predicted enantiomeric ratio (er) of 94:6 (88% ee) for lithiation of **70** with **58**·*i*-PrLi.



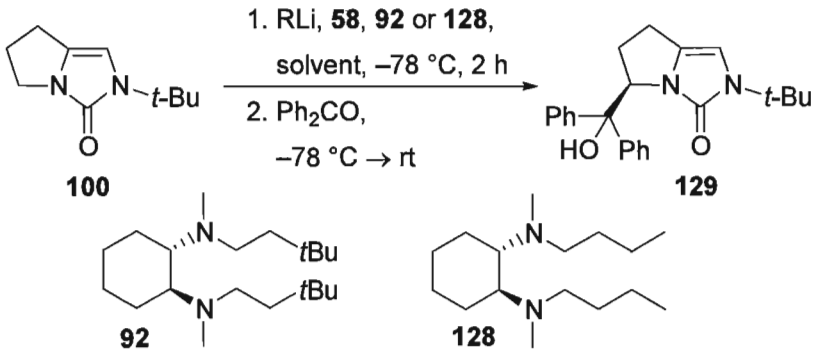
TS1: pro-*S*



TS2: pro-*R*

Figure 17. TS1 and **TS2** showing key contact distances between reagent and substrate[70] (red = oxygen, blue = nitrogen, white = hydrogen, grey = carbon; purple = lithium)

Unlike the saturated urea **105**, unsaturated urea **100** does not contain a chiral center to induce stereoselectivity during lithiation reaction. As the model above shows, the use of chiral ligands **92** and **128**, in addition to **58**, may be required to mediate an asymmetric lithiation with high selectivity. The intermediate carbanion is expected to be configurationally stable until it is trapped with electrophiles. Besides the chiral ligands, solvents and alkyllithium size will likely have a significant influence on the reaction outcome.[36]



Scheme 28: Chiral diamines for the asymmetric lithiation-substitution of **100**

For the sake of enantiomeric purity determination, racemic products were prepared by lithiation of **100** with *i*-PrLi/TMEDA in Et_2O at –78 °C before electrophile quench. The yields of substituted products obtained in this manner ranged form 60-70%.

Due to ease of chiral HPLC separation, the benzophenone adduct **129** was selected as the product with which to screen the enantioselectivity of the process under conditions employing various alkyllithiums, solvents and chiral diamines (**Table 5**). Diamines **92** and **128** were prepared following a procedure in Alexakis[59].

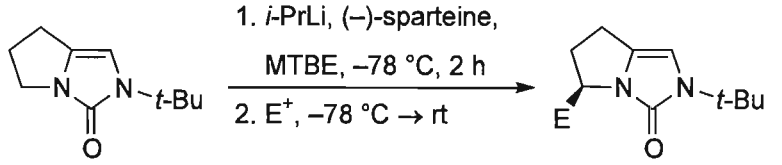
Table 5. Lithiation-substitution optimization for benzophenone adduct **129**

L*	RLi	solvent	yield, %	er (% ee), **129**
(–)-sparteine	*s*-BuLi	Et_2O	73	68.5:31.5 (37)
(–)-sparteine	*i*-PrLi	Et_2O	64	82:18 (64)
(–)-sparteine	*i*-PrLi	MTBE	67	90.5:9.5 (81)
(–)-sparteine	*i*-PrLi	PhMe	8	82.5:17.5 (65)
92	*i*-PrLi	Et_2O	60	14.5:85.5 (71)
92	*i*-PrLi	MTBE	62	15.5: 84.5 (69)
92	*i*-PrLi	PhMe	44	14.5:85.5 (71)
128	*i*-PrLi	Et_2O	52	27.5:82.5 (45)

As shown in **Table 5**, the best result was obtained using the combination of (–)-sparteine and *i*-PrLi in methyl *tert*-butyl ether (MTBE) solvent, which after benzophenone quench gave **129** in 67% yield and 81% ee. Performing the reaction with *i*-PrLi and (+)-sparteine surrogate **92** in Et_2O gave the antipode of **129** in 60% yield and 71% ee. It is interesting to note the large difference in enantioselectivity observed between *s*-BuLi and *i*-PrLi in the first two entries of the table (37 versus 64% ee, respectively). A similar observation was made in the lithiation of urea **70** previously. It is unclear why two very similar alkyllithiums would give such different enantioselectivities in this reaction.

Applied to other electrophiles (**Scheme 29**), the optimum *i*-PrLi/(–)-sparteine/MTBE conditions gave Me, allyl, and stannyl derivatives **130-132** in higher enantiomeric purity (94:6 to 99:1 er; 88-98% ee) and yields ranging from 61-76%. Phenylation according to the procedure described for *N*-Boc pyrrolidine afforded **133** in lower yield (30%), but

similar enantiomeric purity (93.5:6.5 er; 87% ee). The range of ee's for the products (81-98% ee) is good agreement with the transition state modeling of this reaction (88% ee).



100 **129-133**

E^+	E	product	yield, %	er (% ee)
Ph_2CO	Ph_2COH	**129**	67	90.5:9.5 (81)
Me_2SO_4	Me	**130**	63	97:3 (94)
allyl bromide[a]	allyl	**131**	76	94:6 (88)
$SnMe_3Cl$	$SnMe_3$	**132**	68	99:1 (98)[b]
PhBr[c]	Ph	**133**	30	93.5:6.5 (87)

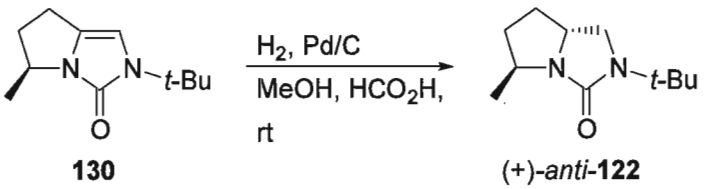
[a] via CuCN·2LiCl transmetalation.

[b] after transmetalation (*n*-BuLi, THF, –100 °C, 1 h) and Me_2SO_4 quench.

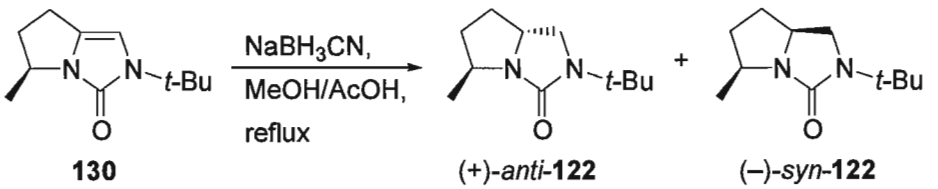
[c] via $ZnCl_2$ transmetalation and $Pd(OAc)_2$ / HBF_4·P(*t*-Bu)$_3$ coupling.

Scheme 29. Asymmetric lithiation-electrophile quench of **100**

An attempt to confirm of the absolute stereochemistry of **130** by hydrogenation to *syn*-**122** (H_2, Pd/C, HCO_2H/MeOH) was precluded by the formation of the *anti*-**122** stereoisomer (**Scheme 30**). The absolute stereochemistry of **130** was instead determined by reduction of the enamine ($NaBH_3CN$, MeOH/AcOH, reflux), which gave a mixture of *anti*- and *syn*-**122** (**Scheme 31**). After careful purification, it was found that *syn*-**122** had the same specific rotation ($[\alpha]_D^{20}$ –4) as **122** derived from saturated urea **105** ($[\alpha]_D^{20}$ –4.4). The relative stereochemistry of *anti*-**122** was verified by 1-D NOE experiments using the method described previously (**Figure 18**).[36]



Scheme 30. Hydrogenation of **130**



Scheme 31. Reduction of **130** to *syn*/*anti*-**122**

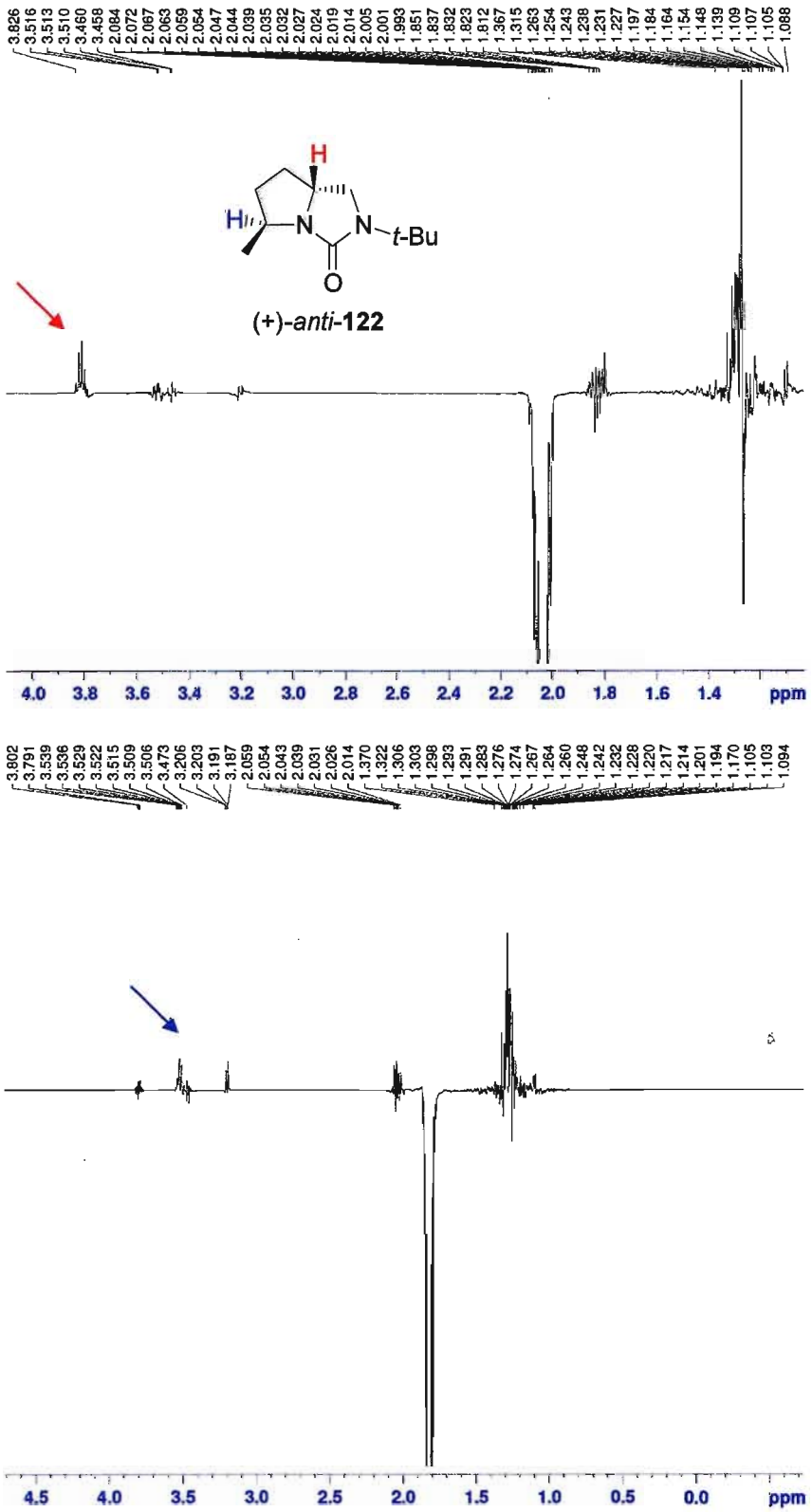


Figure 18. NOE studies of *anti*-**122**

The relative stereochemistry of the *syn*- and *anti*-**122** can also be assigned based on the ^{13}C-NMR data. It has been reported by Hudlicky and others that methyl groups of bicyclic ketones such as **137**[71, 72] show different chemical shifts in ^{13}C NMR depending on the relative stereochemistry of the compound. As shown in **Figure 19**, the methyl group of *syn*-**137** is at 16.4 ppm while the methyl group of *anti*-**137** appears further downfield at 21.3 ppm. The same trend is observed for *syn*-**122** and *anti*-**122**, where the signals appear at 18.2 and 22.5 ppm, respectively. These results corroborate the NOE stereochemical assignments made previously.

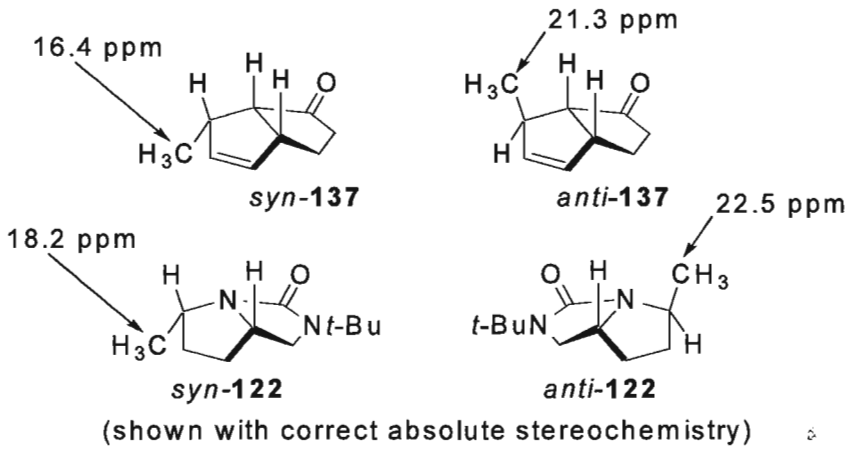
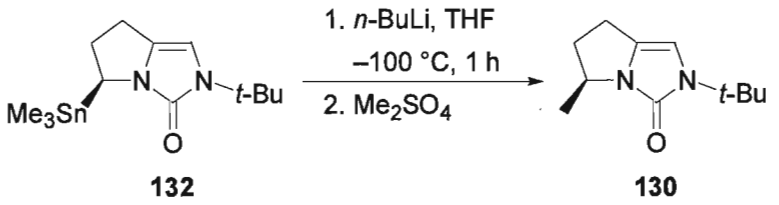


Figure 19. Comparison of the ^{13}C NMR methyl shifts in **137** and **122**

In addition, transmetalation of stannane **132** (*n*-BuLi, THF, –100 °C, 1 h) and subsequent quench with Me_2SO_4 gave **130** with the same optical rotation as **130** made directly from **100**. This results shows that the enantioselectivity of the process originates from asymmetric deprotonation step with *i*-PrLi/(–)-sparteine-mediated and allows for the assignment of the relative stereochemistry for all products **129-133**.

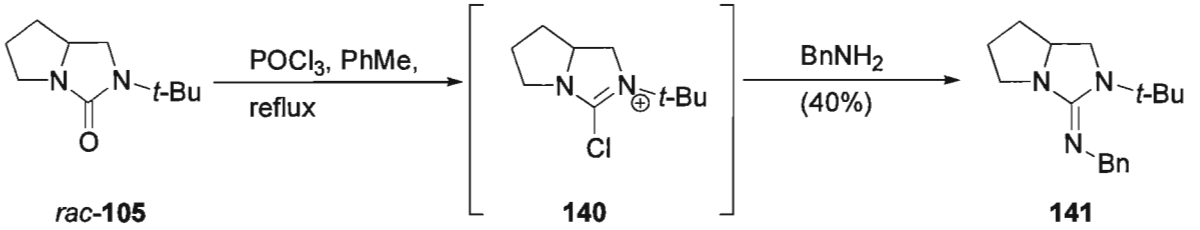


Scheme 32. Transmetalation of **132** to produce **130**

2.4. Manipulation of Substituted and Unsubstituted Ureas by Phosphorus Oxychloride Activation

2.4.a. Conversion to Guanidines

Following a general procedure by Ishikawa,[11, 13] using oxalyl chloride to convert the urea to guanidine **141** was unsuccessful. However, the saturated urea *rac*-**105** was successfully converted to guanidine **141** using 1 equivalent of $POCl_3$ in refluxing toluene.[73] In this process, the intermediate 3-chloroimidazolinium salt **140** was not isolated but treated with benzylamine in situ to afford the product, an air-stable yellow solid, in 40% overall yield.

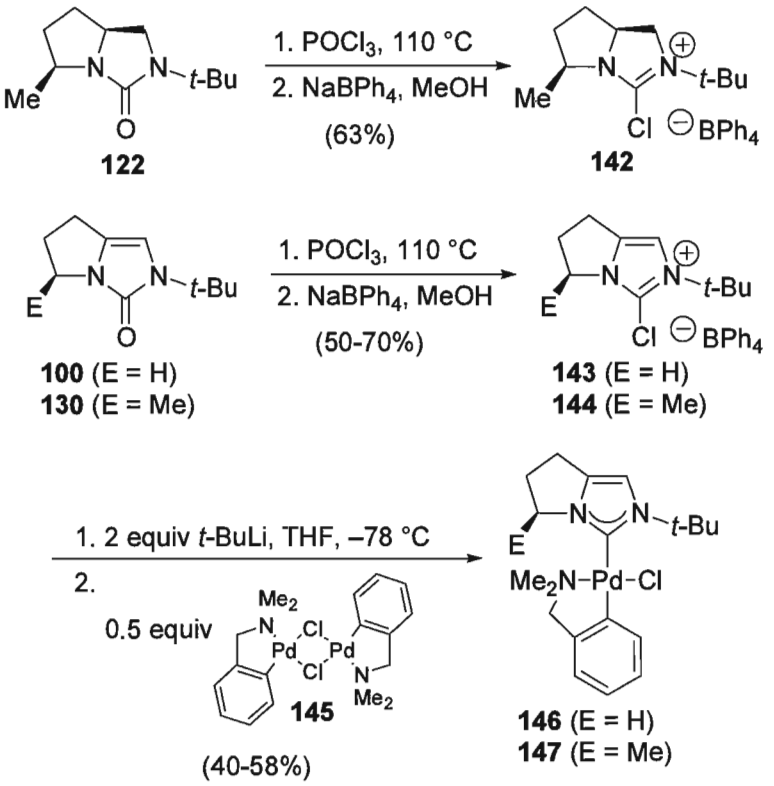


Scheme 33. Synthesis of guanidine **141** from *rac*-**105**

2.4.b. NHCs and Palladium(II) Complexes

The same approach of $POCl_3$ activation was used with also used with alpha chiral substituted ureas, with minor modifications of the procedure. First, the ureas **122**, **100** and **130** were converted to the chloro-imidazol(in)ium salts **142-144** by heating in neat $POCl_3$. The intermediate salts were then isolated after anion exchange with sodium tetraphenylborate ($NaBPh_4$). Compounds **143** and **144** were converted directly to NHCs by chlorine-lithium exchange with *t*-BuLi at low temperature. In principle, this exchange procedure should work equally well for 3-chloro-imidazolinium salt **142** according to a procedure reported by Hong in 2009.[74]

To trap carbenes derived from **143** and **144**, an inexpensive Pd dimer **145**[75] was prepared according to a literature procedure. This simple procedure involved mixing $PdCl_2$ with dimethylamine in methanol under argon atmosphere for 4 hours. The precipitate was then collected and recrystallized from benzene/hexane.[74] Addition of **145** to either **143** or **144** afforded the new Pd(II) complexes **146** and **147** in 40-58%. Product **147** was a 10:7 mixture coordination isomers, which were not separable by column chromatography.

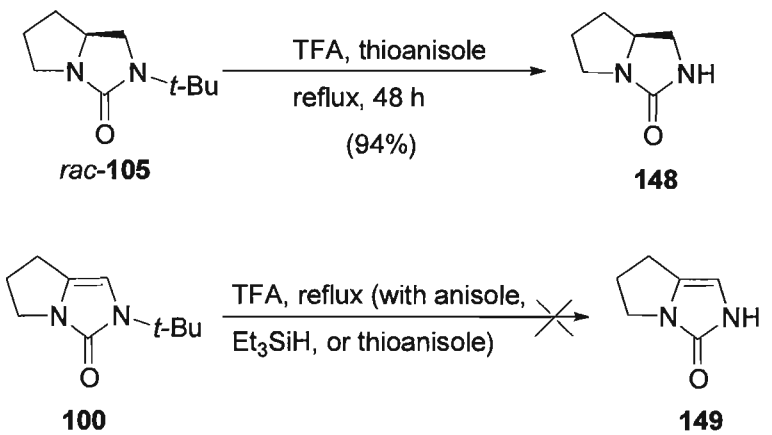


Scheme 34. Imidazol(in)ium salts of **142-144** and Pd complexes **146** and **147**

2.4.c. Manipulation to Biologically Active Compounds

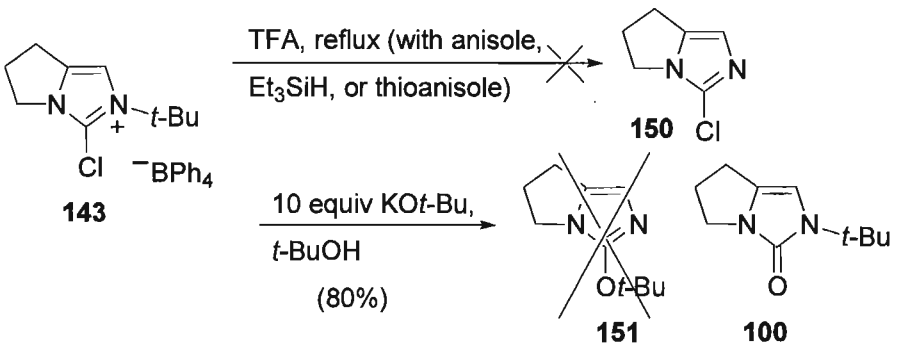
As mentioned earlier in the Introduction, chiral pyrroloimidazoles have been reported to have inhibitory effects on enzymes such as aldosterone synthase, but they have not been prepared in an asymmetric manner. To convert the unsaturated compound **100** to this imidazole derivative, the *t*-butyl group would need to be removed. This was possible with the saturated urea **105** by heating trifluoroacetic acid (TFA) to produce hexahydro-pyrrolo[1,2-c]imidazol-3-one **148**. However, this procedure did not provide the desired product **149** when **100** was subjected to the same conditions. Shi et al. reported *N*-dealkylation of other saturated ureas using mixtures of methanesulfonic acid in refluxing

hexane,[18] however this again did not produce the desired product. Additives such as anisole and thioanisole were utilized in conjunction with TFA, but to no avail. The reluctance of **106** dealkylate under acidic conditions may be a consequence of the enamine moiety, which probably picks up a proton rendering the *t*-Bu group unreactive.



Scheme 35. Acid promoted removal of *N*-*t*-Bu group in *rac*-**105**

Removal of the *t*-butyl group was also attempted on imidazolium salt **143**. Even in this case, only starting material was recovered with no sign of product **150**. Only strong bases such as KO*t*-Bu were had any effect on **143**. Initially it was thought that a substitution of the chloride with *N*-dealkylation had occurred to give **151**. However, closer inspection of the data revealed the formation of urea **100**, which must have formed from attack of adventitious water or hydroxide in the reaction mixture followed by equilibration to the carbonyl. In any case, the risk of racemization of alpha aryl products such as **133** under strongly basic conditions dissuaded attempts to make pyrroloimidazole products with potential biological activity.



Scheme 36. Attempts to remove the *t*-Bu group in **143**

3. Conclusions and Future Work:

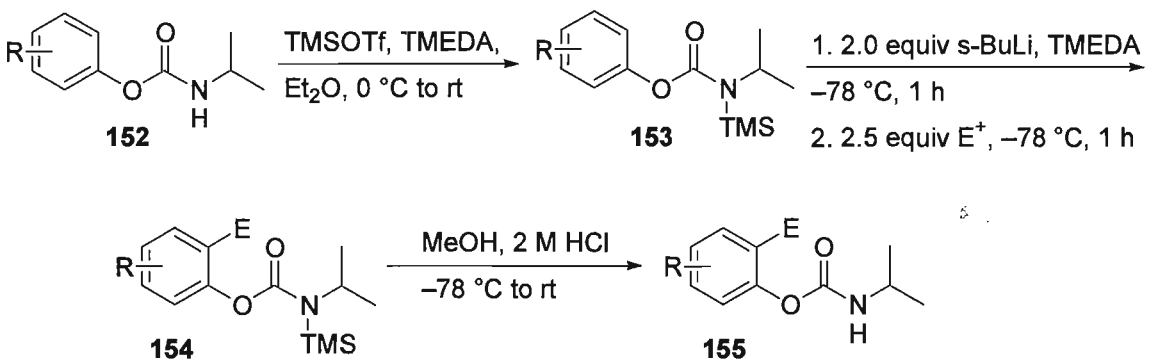
In summary, the lithiation-substitution of the chiral urea **105** with *i*-PrLi or *s*-BuLi and TMEDA in Et_2O was highly diastereoselective. Groups introduced at the 5-position included carbon substituents such as (diphenylhydroxy)methyl, methyl, allyl and carboxyl. Silyl and stannyl derivatives were made with equal facility. Yields for all products ranged from 50-80%. The *syn* stereochemistry of the products was verified by 2-D NOESY and 1-D NOE selective irradiation experiments.[36]

After screening a number of ligand (chiral diamine)-solvent-alkyllithium for unsaturated urea **100**, it was found that *i*-PrLi/(–)-sparteine in MTBE afforded the benzophenone adduct in 67% yield and 81% ee. This set of conditions gave access to Me, allyl, stannyl and Ph derivatives in 87-98% ee. The phenyl adduct was formed is lower 30% yield compared to the remaining derivatives (63-76% yield). The stannyl derivative was determined to have the highest enantiomeric purity of the series, even after transmetalation with *n*-BuLi at –100 °C and Me_2SO_4 quench. In addition, the absolute

stereochemistry of the products was determined by reduction of **130** to *syn*-**122**, which had the same sign of optical rotation as **105**-derived **122**.[36]

Transformation of saturated **105** and unsaturated urea **100** products into guanidines or *N*-heterocyclic carbenes was possible by formation of imidazol(in)ium salts using $POCl_3$ as a stoichiometric reagent or as solvent. Unsaturated ureas **100** and **130** served as immediate precursors to Pd-complexes **146** and **147** by chlorine-lithium exchange of the isolated 3-chloro-imidazolium salts.[36]

Although headway was made towards the synthesis of aldosterone synthase inhibitors, the unforeseen difficulties involving the removal of the *t*-Bu group precluded formation of the desired products. This problem may be addressed by invoking a latent-*N*-silyl protecting group strategy as reported by Hoppe for secondary carbamates, and summarized in **Scheme 37**.[76]

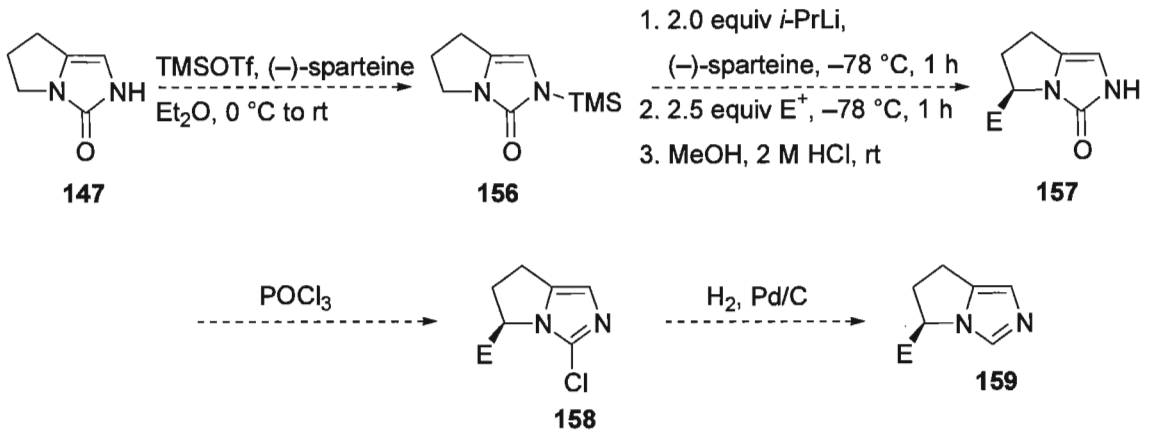


152 **153** **154** **155**

Scheme 37. Hoppe's procedure of in situ *N*-silylation of carbamates

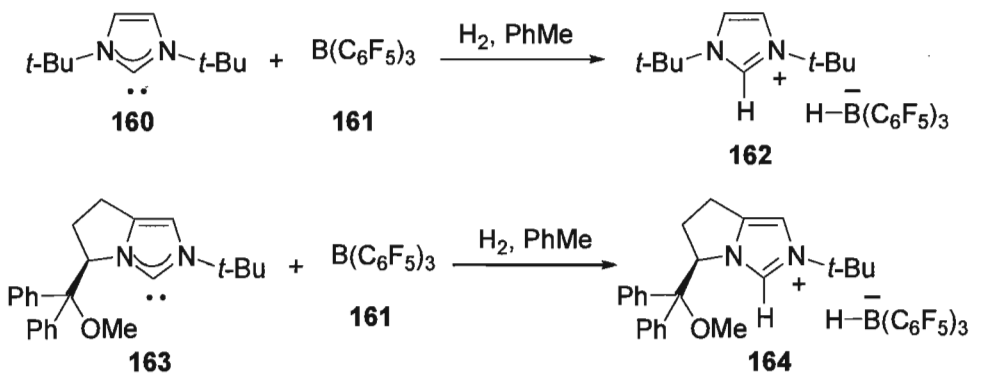
Applying the same principle, **147** can be protected in situ to give **156**, which may undergo asymmetric lithiation-substitution to give secondary urea **157** after treatment with dilute acid. Products **157** should be easy to convert to chiral 3-chloro-

pyrroloimidazoles **158** and hence to imidazoles **159** by standard dechlorination procedures (H_2, Pd/C). Derivatives **159** where E = Ar would be biologically active.



Scheme 38. Alternative in situ *N*-silyl protection-deprotection route to pyrroloimidazoles

Finally, even without the removal of the *t*-butyl group, this annulated system can also be useful in synthesis. Stephan and co-workers have shown that bis-*t*-Bu NHC **160** forms a "Frustrated" Lewis Pair (FLP) with the Lewis acid $B(C_6F_5)_3$ (**161**) that is able to activate small molecules such as H_2 to give imidazolium borohydride **162**.[77, 78] It is conceivable that bulky derivatives of **100**, such as ether **163**, may also participate in this chemistry to give salt **164**. To the best of our knowledge, this would be the first example of an FLP reaction involving a chiral NHC.



Scheme 40. NHCs as Lewis bases in FLP activation of hydrogen[77, 78]

4. Experimental:

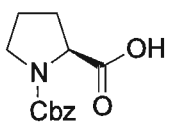
General. All reagents were purchased from Aldrich, Fisher Scientific, Acros or Strem and used as received unless otherwise indicated. Tetrahydrofuran (THF) and diethyl ether (Et_2O)was freshly dried and distilled over sodium/benzophenone ketyl under an atmosphere of nitrogen. MTBE was distilled over $LiAlH_4$ under an argon atmosphere. Dimethyl sulfate (Me_2SO_4), TMEDA, bromobenzene and TMSCl were all distilled over calcium hydride (CaH_2). Allyl bromide was washed with saturated aqueous sodium bicarbonate ($NaHCO_3$), water, and dried over magnesium sulfate ($MgSO_4$), followed by distillation under argon atmosphere. Toluene was distilled over sodium under nitrogen. Dichloromethane was distilled over CaH_2 under nitrogen. Alkyllithium reagents were titrated against *N*-benzylbenzamide to a blue endpoint.[79] All reactions were performed under argon in flame- or oven-dried glassware using syringe-septum cap techniques unless otherwise indicated. TLC plates were stained with phosphomolybdic acid. Column chromatography was performed on silica gel 60 (70-230 mesh). NMR spectra were obtained on Bruker Avance 300 or Avance 600 instruments and are referenced to TMS or to the residual proton signal of the deuterated solvent for ^1H spectra, and to the carbon multiplet of the deuterated solvent for ^{13}C spectra according to values given in *Spectrometric Identification of Organic Compounds, Seventh Edition*, p. 200 and p. 240.[80] FTIR spectra were recorded on an ATI Mattson Research Series spectrometer. Low and high-resolution mass spectral data were obtained on a Kratos Concept 1S Double Focusing spectrometer. Enantiomeric ratios were determined on an Agilent 1100 HPLC system using Chiralpak AS-H or Chiralcel OD-H columns and were compared

against racemic material; compounds were detected at 254 nm unless otherwise indicated. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA, USA. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Isopropyllithium[81]

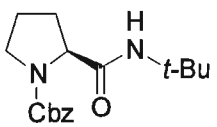
Lithium granules (5.73 g, 826 mmol) were weighed into a Petri dish filled with paraffin oil, and while covered in the oil, the lithium was flattened carefully with a hammer and cut to tiny pieces. After quickly rinsed off the oil with pentane, the lithium was placed in a two-necked round bottom flash fitted with a condenser and an additional funnel. The whole system was immediately flushed with argon. Pentane (100 mL) was added to the flask and the mixture was heated to reflux. A mixture of chloropropane (31.4 mL, 0.344 mol) and MTBE (0.41 mL, 3.44 mmol) was added dropwise to the lithium/pentane mixture over 70 mins with stirring. After the addition was completed, the mixture was allowed to reflux for 20 min and then cooled to rt. At rt, stirring was stopped and the salts were allowed to settle over 42 h. The supernatant solution was transferred to a 100 mL serum bottle under argon. The residual lithium powder and salts were cooled to 0 °C and quenched by slow addition of absolute EtOH (30 mL), 95% EtOH (30 mL) and water (10 mL).

(–)-(*S*)-Pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester (109) [82]



This compound was prepared following a literature procedure. A three-neck round bottom flask containing a well stirred solution of L-proline (23.0 g, 0.2 mol) in 2 M NaOH (100 mL) at 0 °C was equipped with two additional funnels and a thermometer adapter. To this solution was added dropwise 4 M NaOH (70 mL) and CbzCl (36.4 mL, 0.24 mol) simultaneously over one hour. The resulting solution was stirred at 0 °C for another hour and then it was washed with Et_2O (2 x 50 mL). The aqueous layer was then acidified to pH 1 using 6 M HCl, and it was saturated with Na_2SO_4 prior to extraction with EtOAc (4 x 100 mL). The combined organic layer was washed once with brine, dried over Na_2SO_4 and the excess organic solvent was removed in *vacuo* to give **109** as a wax-like colorless and clear product (45.85 g, 92%); $[\alpha]_D^{20}$ –40.2 (*c* 2, abs. EtOH); lit[82]: $[\alpha]_D^{20}$ –39.9 (*c* 2, abs. EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 12-10 (br, 1H), 7.36-7.31 (m, 5H), 5.23-5.13 (m, 2H), 4.34-4.36 (m, 1H), 3.61-3.42 (m, 2H), 2.32-1.92 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 177.2, 176.4, 155.4, 154.5, 136.3, 136.3, 128.3, 128.3, 127.9, 127.7, 127.5, 67.3, 67.0, 59.2, 58.7, 46.8, 46.5, 30.7, 29.5, 24.1, 23.3. (lit[83]: ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.8, 176.3, 155.1, 154.3, 136.0, 128.1, 128.0, 127.6, 127.5, 127.3, 127.2, 67.0, 66.8, 58.9, 58.3, 46.6, 46.2, 30.5, 29.4, 23.9, 23.1.)

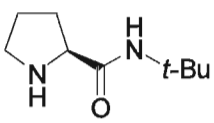
(–)-(*S*)-1-Benzyloxycarbonyl-2-*tert*-butylaminocarbonylpyrrolidine (110) [67]



This compound was prepared according to literature procedure. To a stirred solution of **109** (27.1 g, 0.11 mol) and triethylamine (15.3 mL, 0.11 mol) in THF at 0 °C was added ethyl chloroformate (10.5 mL,

0.11 mol) dropwise with vigorous stirring. The resulting white slurry was stirred for another 30 minutes and treated with freshly distilled *t*-butylamine (11.7 mL, 0.11 mol) over 15 min. After 1 h, the reaction was mixture was filtered and the rinsed thoroughly with EtOAc (20 mL). The solvents were removed on a rotary evaporator and the crude product was redissolved in ethyl acetate (100 mL) and washed with water (50 mL), aqueous sodium bicarbonate solution (50 mL) and brine (50 mL). The excess solvent was removed in *vacuo* to give a colourless solid (30 g, 90%), which was then crystallized over EtOAc (20 mL) to give a colourless needles **110** (27 g, 80%). $[\alpha]_D^{20}$ –92.0 (*c* 1, $CHCl_3$); lit[84]: $[\alpha]_D^{20}$ –90.2 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): rotamers, δ 7.61 (b, 5H), 6.55 (b, 0.5), 5.65 (b, 0.5), 5.26-5.05 (b, 2H), 4.19 (b, 1H), 3.50 (b, 2H), 2.30-2.87 (b, 2H), 1.29-1.21 (b, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 128.4, 128.1, 67.2, 61.1, 50.9, 45.7, 25.8.

(–)-(*S*)-2-*tert*-butylaminocarbonylpyrrolidine (111) [67]



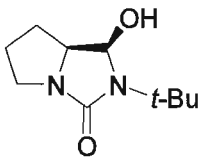
Prepared according to a literature procedure. A solution of **110** (5.00 g, 0.016 mol) in freshly distilled cyclohexene (2.53 mL, 0.025 mol) was stirred under argon atmosphere. To this solution was added 10% Pd/C (100 mg, 2% wt/wt) and the mixture was heated to reflux for 45 minutes or until TLC indicated consumption of starting material. The reaction mixture was filtered through a pad of Celite and rinsed with abs. EtOH (5 mL). Removal of organic solvents in *vacuo* provided the desired product as a colorless solid (2.60 g, 96%). The crude solid was recrystallized from hexane (*ca.* 10 mL) to give colorless and transparent rods (2.30 g, 85%). $[\alpha]_D^{20}$ – 77.0 (*c* 1.0, abs. EtOH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (b, 1H), 3.67-3.62 (m, 1H),

3.05-2.97 (m, 1H), 2.90-2.85 (m, 1H), 2.48 (b, 1H), 2.17-2.05 (m, 1H), 1.92-1.82 (m, 2H), 1.77-1.67 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.3, 61.1, 49.9, 47.1, 30.6, 28.7, 26.1.

(–)-2-*tert*-Butyl-7a*S*-hexahydropyrrolo[1,2-c]imidazol-3-one (105). To a solution of the pyrrolidine **111** (1.00 g, 5.88 mmol) in dry DME (20 mL) was added $LiAlH_4$ (939 mg, 24.5 mmol) in three portions. The resulting mixture was heated at reflux for 15 h under argon, cooled to 0 °C, and worked up with sat. aq. Na_2SO_4 solution (*ca.* 20 mL). After warming to room temperature, the solids were removed by filtration, rinsing with CH_2Cl_2 (10 mL). The separated organic layer was washed with brine, dried over anhyd. Na_2SO_4 and filtered into a round bottomed flask. This solution of volatile diamine was degassed by bubbling argon through it for 15 min, and then transferred by cannula into a flame-dried round-bottomed flask under argon. To this solution was added triethylamine (2.46 mL) and a solution of triphosgene (1.90 g) in CH_2Cl_2 (10 mL). The resulting cloudy mixture was stirred at room temperature for 15 h, worked up with water, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellowish oil. Column chromatography (7:3 hexane/EtOAc, silica gel) gave urea **105** as a colorless oil (500 mg, 47% from **111**); $[\alpha]_D^{20}$ –81 (*c* 1.0, $CHCl_3$); (λ = 205 nm, Chiralcel OD-H; eluent: 90:10 hexanes/*i*-PrOH, 1.0 mL/min) determined >99:1 er [t_R(major) = 6.64 min, t_R(minor) is undetectable]; IR (KBr, neat) υ_{max} 2969, 2902, 1691, 1481, 1406, 1273, 1256 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67-3.45 (m, 3H), 3.27 (d, 1H, J = 7.5 Hz), 2.99-2.91 (m, 1H), 1.93-1.82 (m, 2H), 1.80-1.65 (m, 1H), 1.33 (s, 9H), 1.39-1.22 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ

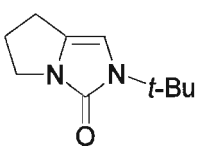
163.7, 55.6, 52.9, 45.9, 45.3, 30.4, 27.7, 24.9; EIMS [*m/z*(%)] 182 (M^+, 9), 167 (M^+-CH_3, 100), 60 (20), 57 (47); HRMS (EI) calcd for $C_9H_{15}N_2O$: 167.1184; found 167.1177.

(–)-2-*tert*-Butyl-1*R*-hydroxy-7a*S*-hexahydropyrrolo[1,2-c]imidazol-3-one (113). To a



stirred suspension of $LiAlH_4$ (400 mg, 0.10 mmol) in THF (40 mL) at 0 °C was added, dropwise, a solution of Cbz-prolinamide **111** (3.90 g, 0.013 mol) in THF (10 mL). The resulting suspension was allowed to warm to room temperature and stirred for 30 min. After cooling to 0 °C, the mixture was worked-up by dropwise addition of sat. aq. Na_2SO_4 solution (5 mL) and allowed to warm to room temperature. The solids were removed by filtration, rinsing with CH_2Cl_2 (2 x 5 mL). The resulting solution was dried over anhyd. Na_2SO_4, filtered again, and concentrated in *vacuo* to give a semi-solid mixture that was Kugelrohr distilled (0.1 mmHg, 70 °C for 30 min) to remove benzyl alcohol, leaving a colorless solid (2.00 g). The hemiaminal (**113**) was crystallized from EtOAc (20 mL, 891 mg, 72%). mp 196-199 °C (EtOAc); $[\alpha]_D^{20}$ –0.356 (*c* 0.5, acetone); IR (KBr) υ_{max} 3228, 2970, 2945, 2879, 2802, 2735, 1657, 1415, 1124, 1026 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.30 (dd, 1H, *J* = 8.4, 7.2 Hz), 3.89 (q, 1H, *J* = 6.6 Hz), 3.56-3.51 (m, 1H), 3.06-3.02 (m, 1H), 2.26 (d, OH, *J* = 8.4 Hz), 2.01-1.95 (m, 1H), 1.95-1.90 (m, 2H), 1.84-1.79 (m, 1H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 161.0, 80.8, 60.7, 53.2, 45.5, 28.8, 27.2, 24.7; Anal. calcd for $C_{10}H_{18}N_2O_2$: C, 60.58, H, 9.15; found C, 60.84, H, 9.35.

2-*tert*-Butyl-2,5,6,7-tetrahydropyrrolo[1,2-c]imidazol-3-one (100). To a stirred

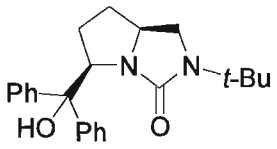


suspension of $LiAlH_4$ (400 mg, 0.10 mmol) in THF (40 mL) at 0 °C was added, dropwise, a solution of Cbz-prolinamide **111** (3.90 g, 0.013 mol) in THF (10 mL). The resulting suspension was allowed to warm to room temperature and stirred for 30 min. After cooling to 0 °C, the mixture was worked-up by dropwise

addition of sat. aq. Na_2SO_4 solution (5 mL) and allowed to warm to room temperature. The solids were removed by filtration, rinsing with CH_2Cl_2 (2 x 5 mL). The resulting solution was dried over anhyd. Na_2SO_4, filtered again, and concentrated in *vacuo* to give a semi-solid mixture that was Kugelrohr distilled (0.1 mmHg, 70 °C for 30 min) to remove benzyl alcohol, leaving a colorless solid. To this solid was added 0.1 M aq. HCl (130 mL), and the suspension was allowed to stir for 1 h at rt or until all the solid had dissolved. The acidic solution was extracted with CH_2Cl_2 (1 x 200 mL, 2 x 100 mL) and the combined organic phase was dried over anhyd. Na_2SO_4, filtered, concentrated and dried under high vacuum to give **100** as a colorless solid (2.05 g, 87%). Recrystallization from hexane (60 mL) gave analytically pure material as needle-shaped crystals (two crystallizations: 1.80 g, 76%); mp 133-136 °C (hexane); UV (*i*-PrOH) λ_{max} 218 nm, ε = 2401 L/mol/cm; IR (KBr) υ_{max} 3126, 2977, 2964, 1666, 1631, 1421, 1355, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.97 (s, 1H), 3.65 (t, 2H, J = 6.9 Hz), 2.66 (t, 2H, J = 6.9 Hz), 2.35 (t, 2H, J = 7.2 Hz), 1.51 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 150.0, 124.7, 99.0, 54.6, 41.9, 28.3, 27.9, 22.8; EIMS [*m/z*(%)] 180 (M^+, 17), 124 (100), 69 (15); Anal. calcd for $C_{10}H_{16}N_2O$: C, 66.63, H, 8.95; found C, 66.83, H, 9.11.

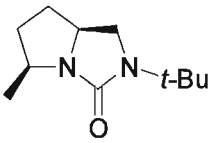
General Procedure A (lithiation-substitution of (105). A solution of urea **105** (1 equiv.) and TMEDA (1.2 equiv) in Et_2O (0.10 M) was cooled to −78 °C. After 15 min, this pre-cooled solution was treated dropwise with *s*-BuLi (1.2 equiv., solution in cyclohexane) and the resulting pale yellow transparent solution stirred at −78 °C for 2 h before dropwise addition of the desired electrophile (1.5 equiv.). The reaction was allowed to warm up to room temperature over 16 h. *Standard Workup*: The reaction

mixture was worked up by cooling in an ice bath, followed by addition of water (5 mL). After separation of the layers, the aqueous phase was extracted with Et_2O (3 x 10 mL), and the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography.

(+)-2-*tert*-Butyl-5*R*-(diphenylhydroxy)methyl-7a*S*-hexahydropyrrolo[1,2-c]imidazol-3-one (121). 

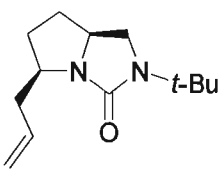
According to General Procedure A, a solution of **105** (89 mg, 0.49 mmol) and TMEDA (0.09 mL, 0.59 mmol) in Et_2O (5 mL) was sequentially treated with *s*-BuLi (0.51 mL, 0.59 mmol) and a solution of benzophenone (135 mg, 0.74 mmol) in THF (2 mL). Standard workup followed by column chromatography (silica gel, 8:2 hexane-Et_2O, R_f = 0.11) gave **121** as a colorless solid (103 mg, 60%); mp 177-179 °C (EtOH); $[\alpha]_D^{20}$ +208 (*c* 1.0, $CHCl_3$); IR (KBr) υ_{max} 3187, 2985, 2956, 2924, 2872, 1660, 1417, 1278, 1156 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, 2H, J = 7.8 Hz), 7.42 (d, 2H, J = 7.8 Hz), 7.29 (t, 2H, J = 7.8 Hz), 7.23 (t, 2H, J = 7.8 Hz), 7.19 (t, 1H, J = 7.8 Hz), 7.15 (t, 1H, J = 7.8 Hz), 7.13 (s, 1H), 4.25 (dd, 1H, J = 9.6, 6.6 Hz), 3.73-3.69 (m, 1H), 3.54 (t, 1H, J = 8.4 Hz), 3.17 (dd, 1H, J = 9.0, 3.0 Hz), 2.10-2.03 (m, 1H), 1.88-1.82 (m, 1H), 1.48-1.42 (m, 1H), 1.40-1.33 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 162.0, 147.7, 146.2, 127.9, 127.7, 126.7, 126.5, 126.3, 126.1, 67.4, 56.7, 53.4, 46.9, 28.8, 27.6, 26.4; Anal. calcd for $C_{23}H_{28}N_2O_2$: C, 75.79, H, 7.74; found C, 75.74, H, 7.85.

(−)-2-*tert*-Butyl-5*S*-methyl-7a*S*-hexahydropyrrolo[1,2-c]imidazol-3-one (122).



According to General Procedure A, a solution of **105** (134 mg, 0.74 mmol) and TMEDA (0.13 mL, 0.89 mmol) in Et_2O (5 mL) was sequentially treated with *s*-BuLi (1.14 mL, 0.89 mmol) and Me_2SO_4 (0.11 mL, 1.11 mmol). Standard workup followed by column chromatography (silica gel, 8:2 EtOAc-hexane, R_f = 0.27) gave **122** as a colorless oil (80 mg, 55%). $[\alpha]_D^{20}$ −4.4 (*c* 1.0, $CHCl_3$); IR (KBr) υ_{max} 2965, 2937, 2872, 1691, 1401, 1364, 1276, 1241 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.68-3.72 (m, 1H), 3.63-3.58 (m, 1H), 3.50 (t, 1H, *J* = 9.0 Hz), 3.11 (t, 1H, *J* = 7.8 Hz), 2.07-2.03 (m, 1H), 1.93-1.88 (m, 1H), 1.66-1.62 (m, 1H), 1.55-1.48 (m, 1H), 1.36 (d, 2H, *J* = 6.6 Hz), 1.31 (s, 10H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 160.6, 56.3, 53.0, 52.9, 48.6, 35.2, 29.7, 27.4, 18.2; EIMS [*m/z*(%)] 196 (M^+, 10), 181 (100); HRMS (EI) calcd for $C_{11}H_{20}N_2O$: 196.1576; found 196.1577.

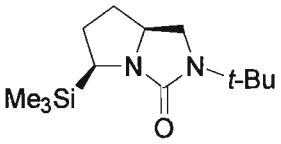
(+)-2-*tert*-Butyl-5*R*-allyl-7a*S*-hexahydropyrrolo[1,2-c]imidazol-3-one (123).



According to General Procedure A, a solution of urea **100** (87 mg, 0.48 mmol) and TMEDA (0.09 mL, 0.58 mmol) in Et_2O (5 mL) was sequentially treated with *s*-BuLi (0.37 mL, 0.60 mmol) and a solution of CuCN (21 mg, 0.24 mmol) and LiCl (20 mg, 0.48 mmol) in THF (1 mL). After one hour at –78 °C, allyl bromide (0.06 mL, 0.74 mmol) was added to the mixture. Standard workup followed by column chromatography (silica gel, 9:1 hexane-EtOAc, R_f = 0.11) gave **123** as a pale yellow oil; $[\alpha]_D^{20}$ +10.4 (*c* 0.45, $CHCl_3$); IR (KBr, neat) υ_{max} 2972, 2930, 2874, 1686, 1406, 1237 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.80-5.65 (m, 1H), 5.08-4.98 (m, 2H), 3.78-3.67 (m, 1H), 3.55-3.45 (m, 1H), 3.48 (t, 1H, *J* = 8.1 Hz), 3.08 (t,

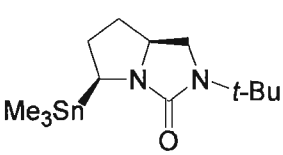
1H, J = 8.1 Hz), 2.92-2.80 (m, 1H), 2.33 (dt, 1H, J = 13.8, 7.0 Hz), 2.00-1.66 (m, 3H), 1.48-1.42 (m, 1H), 1.29 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 160.1, 135.6, 117.1, 56.6, 56.4, 53.0, 48.6, 35.3, 32.1, 29.6, 27.5; EIMS [*m/z*(%)] 222 (M^+, 6), 207 (15), 181 (53), 125 (100), 57 (24); HRMS (EI) calcd for $C_{13}H_{22}N_2O$: 222.1732; found 222.1735.

(–)-2-*tert*-Butyl-5*S*-trimethylsilyl-7a*S*-hexahydropyrrolo[1,2-c]imidazol-3-one (124).



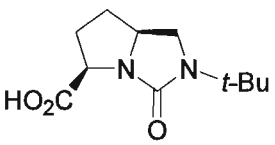
According to General Procedure A, a solution of **105** (69 mg, 0.38 mmol) and TMEDA (0.07mL, 0.46 mmol) in Et_2O (4 mL) was treated sequentially with *s*-BuLi (0.34 mL, 0.46 mmol) and TMSCl (0.07 mL, 0.58 mmol). Standard workup followed by column chromatography (silica gel, 8:2 hexane-Et_2O, R_f = 0.11) gave **124** as a colorless oil (61 mg, 63%); $[\alpha]_D^{20}$ –52 (*c* 1.2, $CHCl_3$); IR (KBr, neat) υ_{max} 2960, 1695, 1408, 1245 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.59-3.52 (m, 2H), 3.20-3.19 (m, 1H), 2.41 (dd, 1H, J = 10.2, 8.4 Hz), 1.99-1.94 (m, 1H), 1.88-1.83 (m, 1H), 1.65-1.59 (m, 1H), 1.50-1.43 (m, 1H), 1.32 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 162.3, 56.6, 52.7, 50.3, 46.8, 31.3, 27.7, 27.6, –0.85; EIMS [*m/z*(%)] 254 (M^+, 22), 239 (57), 207 (45), 197 (79), 183 (85), 125 (91), 57 (100); HRMS (EI) calcd for $C_{13}H_{26}N_2OSi$: 254.1814; found 254.1803.

(–)-2-*tert*-Butyl-5*S*-trimethylstannyl-7a*S*-hexahydropyrrolo[1,2-c]imidazol-3-one



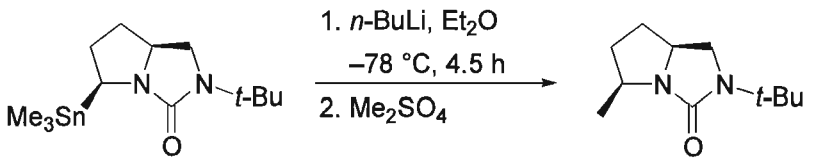
(125). According to General Procedure A, a solution of **105** (90 mg, 0.49 mmol) and TMEDA (0.09 mL, 0.59 mmol) in Et_2O (5 mL) was sequentially treated with *s*-BuLi (0.43 mL, 0.59 mmol) and $SnMe_3Cl$ (0.74 mL, 0.74 mmol, solution in hexane). Standard workup followed by column chromatography

(silica gel, 9:1 hexane-Et_2O, $R_f = 0.11$) gave **125** as a colorless oil (103 mg, 60%); $[\alpha]_D^{20}$ –13 (*c* 1.0, $CHCl_3$); IR (KBr, neat) υ_{max} 2962, 2939, 2908, 2870, 1680, 1412, 1273, 1257 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.61-3.55 (m, 2H), 3.25-3.24 (m, 1H), 2.70 (t, 1H, *J* = 8.1 Hz), 2.04-1.96 (m, 2H), 1.74-1.71 (m, 1H), 1.40-1.38 (m, 1H), 1.34 (s, 9H), 0.12 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.7, 56.2, 52.7, 46.02, 45.99, 31.5, 29.4, 27.6, –7.7; EIMS [*m/z*(%)] 331 (M^+–CH_3, 30), 181 (17), 125 (100), 57 (25); HRMS (EI) calcd for $C_{12}H_{23}N_2O^{120}Sn$: 331.0832; found 331.0834.

(–)-2-*tert*-Butyl-3-oxo-7a*S*-hexahydropyrrolo[1,2-c]imidazole-5*R*-carboxylic acid (126). 

According to General Procedure A, a solution of **105** (69 mg, 0.38 mmol) and TMEDA (0.07, 0.46 mmol) in Et2O (4 mL) was treated sequentially with *s*-BuLi (0.34 mL, 0.46 mmol) and dry ice (bubbled into the reaction after passing through an anhydrous calcium chloride tube). Following standard work-up, a colorless solid **126** was obtained; mp 208-210 °C; $[\alpha]_D^{20}$ –59 (*c* 1.35 , $CHCl_3$); IR (KBr) υ_{max} 2981, 2933, 2884, 2784, 2702, 2567, 2499, 1746, 1633, 1433, 1294 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.15 (b, 1H), 4.17-4.13 (m, 1H), 3.95-3.86 (m, 1H), 3.63 (t, 1H, *J* = 8.4 Hz), 3.38 (t, 1H, *J* = 8.7 Hz), 2.32-2.24 (m, 2H), 2.05-1.96 (m, 1H), 1.85-1.74 (m, 1H), 1.30 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.6, 162.0, 58.6, 55.7, 53.5, 50.3, 33.3, 29.7, 27.5.

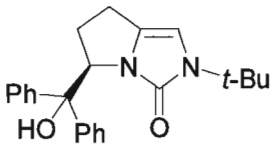
Transmetalation of stannane 125 to 122.



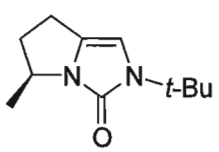
125 (–)-*syn*-**122**

A solution of **125** (96 mg, 0.28 mol) in diethyl ether (6 mL) under argon was cooled to –78 °C, treated with *n*-BuLi (0.15 mL, 2.07 M, 0.31 mmol) and stirred for 4.5 h. The reaction mixture was treated with Me_2SO_4 (0.04 mL, 0.42 mol) and allowed to warm to room temperature over 12 h. Water was added (5 mL) and organic solvents were removed in *vacuo*. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined layer was washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (silica gel, 8:2 EtOAc-hexane, R_f = 0.27) to give *syn*-**122** (12 mg, 22%) as a colorless oil. Physical and spectroscopic data matched that reported for **122** above.

General Procedure B (lithiation-substitution of 100). A solution of (−)-sparteine (1.2 equiv) in MTBE (0.23 M) at –78 °C was treated with *i*-PrLi (1.2 equiv, solution in pentane) and the mixture was stirred for 30 min. A solution of **100** (1 equiv) in MTBE (0.06 M) was then added over 30 min, and the mixture was maintained at –78 °C for 2 h. After addition of the desired electrophile (1.5 equiv) the reaction mixture was allowed to warm slowly to room temperature (about 16 h). *Standard Workup*: The reaction mixture was cooled to 0 °C and treated with distilled water (5 mL), and organic solvents were removed in *vacuo*. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography.

(+)-2-*tert*-Butyl-5*R*-(diphenylhydroxy)methyl-2,5,6,7-tetrahydropyrrolo[1,2-c]imidazol-3-one (129). 

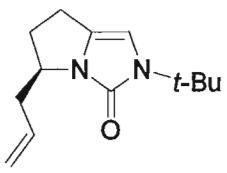
According to General Procedure B, a mixture of (–)-sparteine (0.08 mL, 0.34 mmol) in MTBE (1.5 mL) was sequentially treated with *i*-PrLi (0.25 mL, 0.34 mmol), **100** (50 mg, 0.28 mmol) in MTBE (5 mL) and a solution of benzophenone (78 mg, 0.42 mmol) in MTBE (1 mL). Standard workup followed by column chromatography (silica gel, 8:2 hexanes-EtOAc, $R_f = 0.13$) gave **129** (68 mg, 67%) as a colorless oil; $[\alpha]_D^{20}$ +91 (*c* 1.5, $CHCl_3$); Chiral HPLC analysis (Chiralcel OD-H; eluent: 90:10 hexanes/*i*-PrOH, 1.0 mL/min) determined 90.5:9.5 er, 81% ee [t_R(major) = 13.35 min, t_R(minor) = 23.70 min]; IR (KBr, neat) υ_{max} 3187, 2985, 2956, 2924, 2872, 1660, 1417, 1278, 1156 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.39 (d, 2H, J = 7.2 Hz), 7.34 (t, 2H, J = 7.2 Hz), 7.31-7.24 (m, 3H), 7.24-7.23 (m, 3H), 5.84 (s, 1H), 5.04 (t, 1H, J = 7.2 Hz), 2.52-2.48 (m, 2H), 2.46-2.41 (m, 1H), 2.13-2.08 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 151.2, 144.8, 143.1, 128.1, 127.9, 127.8, 127.5, 127.4, 127.0, 125.8, 99.4, 81.3, 66.2, 55.2, 32.0, 28.2, 21.2; EIMS [*m/z*(%)] 362 (M^+, 6), 180 (100), 124 (69), 105 (24), 77(16), 57 (12). Anal. calcd for $C_{23}H_{26}N_2O_2$: C, 76.21, H, 7.23; found C, 75.95, H, 7.09.

(+)-2-*tert*-Butyl-5*S*-methyl-2,5,6,7-tetrahydropyrrolo[1,2-c]imidazol-3-one (130). 

According to General Procedure B, a mixture of (–)-sparteine (0.14 mL, 0.34 mmol) in MTBE (5 mL) was sequentially treated with *i*-PrLi (0.39 mL, 0.60 mmol), **100** (90 mg, 0.50 mmol) in MTBE (5 mL) and Me_2SO_4 (0.07 mL, 0.75 mmol). Standard workup followed by column chromatography (silica gel, 8:2 EtOAc-hexanes, $R_f = 0.26$) gave **130** as an amorphous glass (61 mg, 63%);

$[\alpha]_D^{20}$ +72 (*c* 1.05, $CHCl_3$); Chiral HPLC analysis (λ = 218 nm, Chiralcel OD-H; eluent: 99:1 hexanes/*i*-PrOH, 0.5 mL/min) determined 97:3 er, 94% ee [t_R(major) = 34.74 min, t_R(minor) = 41.23 min]; IR (KBr, neat) υ_{max} 3044, 2978, 1660, 1631, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.90 (s, 1H), 4.10 (sextet, 1H, *J* = 5.7 Hz), 2.71-2.41 (m, 3H), 1.97-1.86 (m, 1H), 1.47 (s, 9H), 1.40 (d, 3H, J = 6.3 Hz); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 150.0, 124.5, 98.6, 54.5, 51.4, 36.2, 28.3, 21.4, 19.2; EIMS [*m/z*(%)] 194 (M^+, 20), 138 (100), 123 (19); HRMS (EI) calcd for $C_{11}H_{18}N_2O$: 194.1419; found: 194.1417.

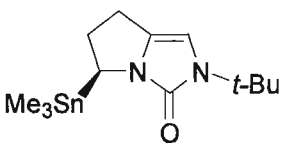
(+)-5*R*-Allyl-2-*tert*-butyl-2,5,6,7-tetrahydropyrrolo[1,2-c]imidazol-3-one (131).



According to General Procedure B a mixture of (–)-sparteine (0.14 mL, 0.6 mmol) in MTBE (5 mL) was sequentially treated with *i*-PrLi (0.39 mL, 0.6 mmol) and **100** (90 mg, 0.5 mmol) in MTBE (5 mL). After 2 h, a solution of CuCN (22 mg, 0.25 mmol) and LiCl (21 mg, 0.5 mmol) in THF (1.5 mL) was added, and after stirring for 1 h at –78 °C, allyl bromide (0.065 mL, 0.75 mmol) was added. Standard workup followed by column chromatography (silica gel, 1:1 EtOAc-hexane, R_f = 0.47) gave **131** as a pale yellow oil (84 mg, 76%) as a colorless oil; $[\alpha]_D^{20}$ +108 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis (λ = 218 nm, Chiralcel OD-H; eluent: 99:1 hexanes/*i*-PrOH, 1.0 mL/min) determined 94:6 er, 88% ee [t_R(major) = 10.77 min, t_R(minor) = 12.60 min]; IR (KBr, neat) υ_{max} 3136, 3076, 2973, 2933, 2872, 1674, 1633, 1412, 1365, 1223 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.89 (s, 1H), 5.77-5.63 (m, 1H), 5.10-5.00 (m, 2H), 4.11-4.04 (m, 1H), 2.70-2.70 (m, 1H), 2.64-2.50 (m, 1H), 2.49- 2.31 (m, 2H), 2.11-2.01 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 149.9, 133.6, 124.8, 117.9, 98.7, 54.8, 54.5, 37.2, 32.8, 28.2, 21.4; EIMS [*m/z*(%)] 220 (M^+, 30), 164

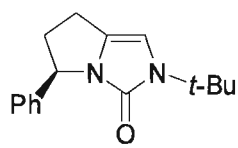
(56), 123 (100), 97 (17), 57 (10); HRMS (EI) calcd for $C_{13}H_{20}N_2O$: 220.1576; found 220.1572.

(+)-2-*tert*-Butyl-5*S*-trimethylstannyl-2,5,6,7-tetrahydropyrrolo[1,2-c]imidazol-3-one



(132). According to General Procedure B, a mixture of (–)-sparteine (0.08 mL, 0.34 mmol) in MTBE (1.5 mL) was sequentially treated with *i*-PrLi (0.25 mL, 0.34 mmol), **100** (50 mg, 0.28 mmol) in MTBE (5 mL) and Me_3SnCl (0.42 mL, 1.0 M solution in hexane, 0.42 mmol). Standard workup followed by column chromatography (silica gel, 8:2 hexane-EtOAc) gave **132** as a colorless oil (65 mg, 68%); $[\alpha]_D^{20}$ +220 (*c* 0.5, $CHCl_3$); IR (KBr, neat) υ_{max} 2973, 2920, 2866, 1668, 1632, 1409, 1365, 1219, 755; ^1H NMR (300 MHz, $CDCl_3$): δ 5.96 (s, 1H), 3.46 (dd, 1H, J = 9.6, 6.9 Hz), 2.66-2.48 (m, 3H), 2.32-2.19 (m, 1H), 1.48 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.1, 125.1, 98.6, 54.4, 41.4, 33.6, 28.3, 24.6, –9.8; EIMS [*m/z*(%)] 344 (M^+, 13), 329 (26), 273 (19), 165 (18), 123 (100); HRMS (EI) calcd for $C_{13}H_{24}N_2O^{120}Sn$: 344.0911; found: 344.0907.

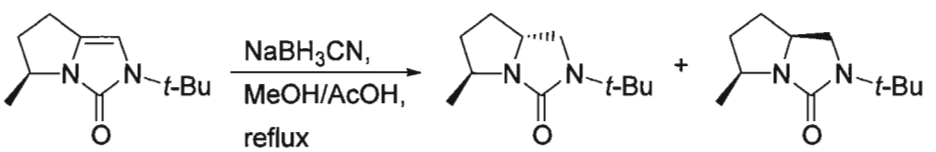
(+)-2-*tert*-Butyl-5*R*-phenyl-2,5,6,7-tetrahydropyrrolo[1,2-c]imidazol-3-one (133).



According to General Procedure B a mixture of (–)-sparteine (0.11 mL, 0.48 mmol) in MTBE (2 mL) was sequentially treated with *i*-PrLi (0.32 mL, 0.48 mmol), **100** (87 mg, 0.48 mmol) in MTBE (5 mL) and 1M $ZnCl_2$ (0.28 mL, 0.28 mmol, solution in THF). After 30 min at –78 °C, the reaction mixture was aged at room temperature for 30 min and then treated with $Pd(OAc)_2$ (5 mg, 5 mol %), *t*-$Bu_3P{\cdot}HBF_4$ (7 mg, 6 mol %) and PhBr (0.042 mL, 0.4

mmol). The mixture was allowed to stir for 16 h at room temperature. Concentrated aqueous NH_3 solution (4 drops) was added and the mixture was stirred for 1 h before filtration through Celite and rinsing with MTBE (2 x 5 mL). The solvents were removed in *vacuo* and the residue was re-dissolved CH_2Cl_2. The organic layer was washed with 0.5 M aq. HCl (2 x 5 mL) and water (5 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. Column chromatography (silica gel, 6:4 hexane-EtOAc, $R_f = 0.10$) gave **133** as a viscous oil that solidified upon standing (31 mg, 30%). $[\alpha]_D^{20}$ +112 (*c* 0.8, $CHCl_3$); Chiral HPLC analysis (Chiralcel OD-H; eluent: 95:5 hexanes/*i*-PrOH, 1.0 mL/min) determined 93.5:6.5 er, 87% ee [t_R(minor) = 10.52 min, t_R(major) = 11.56 min]; IR (KBr, neat) υ_{max} 2974, 2926, 1666, 1632, 1413, 1365 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.21 (m, 3H), 7.15-7.12 (m, 2H), 6.07 (s, 1H), 5.18-5.14 (m, 1H), 2.86-2.65 (m, 3H), 2.32-2.26 (m, 1H), 1.53 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 150.0, 140.9, 128.6, 127.3, 125.6, 125.5, 99.2, 58.0, 54.8, 38.1, 28.4, 21.5; EIMS [*m/z*(%)] 344 (M^+, 13), 329 (26), 273 (19), 165 (18), 123 (100); HRMS (EI) calcd for $C_{16}H_{20}N_2O$: 256.1576; found: 256.1580.

Reduction of 130 to *syn/anti*-122b.



130 (+)-*anti*-**122** (–)-*syn*-**122**

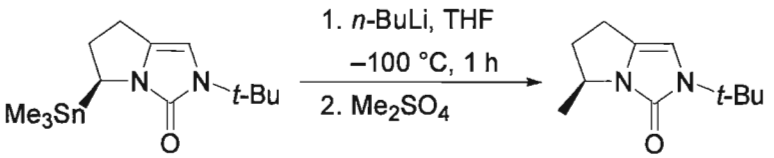
A solution of unsaturated urea **130** (555 mg, 2.86 mmol) in MeOH (14 mL) and acetic acid (4 mL) was treated with sodium cyanoborohydride (757 mg, 11.4 mmol) and heated at reflux for 3 h. After cooling to room temperature, the reaction mixture was poured into

10% aqueous NaOH solution (25 mL). The products were extracted with diethyl ether (5 x 30 mL) and the combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhyd $MgSO_4$, filtered, and concentrated in *vacuo*. Careful column chromatography (300 mL silica gel on a 3.8 cm diameter column, 95:5 CH_2Cl_2/*t*-BuOMe) gave, sequentially, *anti*-**122** (180 mg) as a colorless solid, a mixed fraction of *anti*-**122** and *syn*-**122** (200 mg), and *syn*-**122** (64 mg). The combined yield of *anti*-**122**+*syn*-**122** was 444 mg (79%).

(–)-*syn*-**122.** colorless oil; $[\alpha]_D^{20}$ –4 (*c* 0.1, $CHCl_3$); Spectroscopic data matched (–)-*syn*-**122** obtained directly from urea **17**.

(+)-*anti*-**122.** mp 65-68 °C; $[\alpha]_D^{20}$ +112.2 (*c* 0.4, $CHCl_3$); IR (KBr) 2968, 2916, 2871, 1681, 1411, 1278, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.75 (sextet, 1H, J = 7.2 Hz), 3.49-3.45 (m, 1H), 3.41 (t, 1H, J = 8.1 Hz), 3.17-3.14 (m, 1H), 2.01-1.95 (m, 1H), 1.79-1.74 (m, 1H), 1.31-1.20 (m, 2H), 1.22 (s, 9H), 1.05 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.3, 54.4, 53.9, 52.4, 45.1, 33.7, 31.3, 27.4, 22.5; EIMS [*m/z*(%)] 196 (9), 181 (100); HRMS (EI) calcd for $C_{11}H_{20}N_2O$: 196.1576; found: 196.1578.

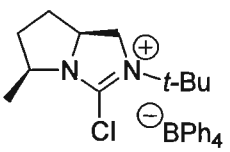
Transmetalation of stannane 132 to 130.



132 **130**

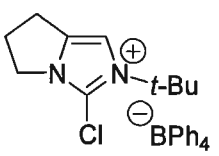
A solution of (+)-**132** (56 mg, 0.16 mmol) in THF (3 mL) at –100 °C was treated dropwise with *n*-BuLi (0.11 mL, 0.21 mmol). The resulting mixture was stirred at –100 °C for 1 h, quenched with Me_2SO_4 (0.023 mL, 0.24 mmol) and allowed to warm to room temperature over 16 h. Standard workup followed by column chromatography (silica gel, 8:2 EtOAc-hexane, R_f = 0.26) gave (+)-**130** (22 mg, 69%). $[\alpha]_D^{20}$ +72 (*c* 0.8, $CHCl_3$); Chiral HPLC analysis (λ = 218 nm, Chiralcel OD-H; eluent: 99:1 hexanes/*i*-PrOH, 0.5 mL/min) determined 99:1 er, 98% ee [t_R(major) = 35.17 min, t_R(minor) = 42.47 min].

(–)-2-*tert*-Butyl-3-chloro-5*S*-methyl-tetrahydropyrrolo[1,2-c]imidazolinium tetraphenylborate (142).

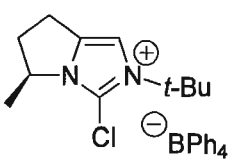


A solution of **122** (19 mg, 0.1 mmol) in $POCl_3$ (0.09 mL) in a sealed tube under Ar was heated to 110 °C for 16 h. The resulting mixture was cooled to room temperature and the excess $POCl_3$ was removed in *vacuo*. The crude mixture was dissolved in MeOH (0.3 mL), and a solution of $NaBPh_4$ (55 mg) in MeOH (0.3 mL) was added dropwise. The resulting precipitate was filtered, washed with cold MeOH and dried under high vacuum to give **142** as a beige powder (33 mg, 63%); mp >230 °C; $[\alpha]_D^{20}$ –107 (*c* 0.5, CH_2Cl_2); IR (KBr) υ_{max} 3159, 3124, 3053, 2985, 2876, 1944, 1880, 1818, 1764, 1586, 1470, 1427 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 7.37-7.31 (m, 8H), 6.93 (t, 8H, J = 7.2 Hz), 6.78 (t, 4H, J = 6.9 Hz); 4.49-4.36 (m, 1H), 4.29 (t, 1H, J = 10.5 Hz), 4.20-4.02 (m, 2H), 2.45-2.32 (m, 1H), 2.17-2.10 (m, 1H), 2.03-1.86 (m, 2H), 1.55 (s, 9H), 1.47 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75.5 MHz, acetone-d_6): δ 165.3 (q, $J^{13}C$-^{11}B = 49.8 Hz), 153.1, 137.4, 126.4 (q, $J^{13}C$-^{11}B = 3.0 Hz), 122.6, 65.8, 61.7, 56.8,

55.4, 37.2, 28.9, 28.8, 19.7. FABMS [*m/z*(%)] 215 (M –BPh_4, 100), 159 (33); HRMS (FAB) calcd for $C_{12}H_{20}N_2{}^{35}Cl$: 215.1315; found: 215.1313.

2-*tert*-Butyl-3-chloro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazolium tetraphenylborate (143). 

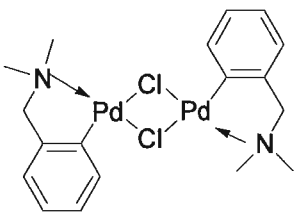
A solution of **100** (50 mg, 0.28 mmol) in $POCl_3$ (0.26 mL) in a sealed tube was heated to 110 °C for 16 h. The resulting mixture was cooled to room temperature and the excess $POCl_3$ was removed in *vacuo*. The crude mixture was dissolved in MeOH (0.5 mL), and a solution of $NaBPh_4$ (105 mg) in MeOH (0.4 mL) was added dropwise. The resulting precipitate was filtered, washed with cold MeOH and dried under high vacuum to give **143** as a beige powder (100 mg, 70%). mp 197-200 °C; IR (KBr) υ_{max} 3138, 3048, 2984, 1600, 1579, 1509, 1477, 1422 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 7.39 (s, 1H), 7.35-7.31 (b, 8H), 6.91 (t, 8H, J = 7.2 Hz), 6.77 (t, 4H, J = 7.2 Hz), 4.16 (t, 2H, J = 7.5 Hz), 2.96 (t, 2H, J = 7.8 Hz), 2.55 (quin, 2H, J = 7.5 Hz), 1.75 (s, 9H); ^{13}C NMR (75.5 MHz, acetone-d_6): δ 164.9 (q, $J^{13}{}_{C}$-$^{11}{}_{B}$ = 49.8 Hz), 139.0, 137.0, 126.0, 122.2, 114.7, 64.1, 49.0, 28.9, 27.8, 24.4; FABMS [*m/z*(%)] 199 (M–BPh_4, 100), 143 (41); HRMS (FAB) calcd for $C_{10}H_{16}{}^{35}ClN_2$: 199.1002; found 199.0996.

(+)-2-*tert*-Butyl-3-chloro-5*S*-methyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazolium tetraphenylborate (144). 

A solution of **130** (54 mg, 0.28 mmol) in $POCl_3$ (0.26 mL) in a sealed tube was heated to 110 °C for 16 h. The resulting mixture was cooled to room temperature and the excess $POCl_3$ was removed in *vacuo*. The crude mixture was dissolved in MeOH (0.5 mL), and a

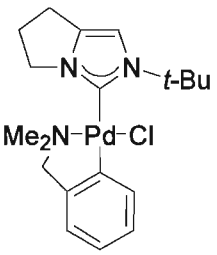
solution of $NaBPh_4$ (144 mg) in MeOH (0.5 mL) was added dropwise. The resulting precipitate was filtered, washed with cold MeOH and dried under high vacuum to give **144** as a brown solid (72 mg, 50%); mp 197-200 °C (MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ +28 (*c* 0.25, CH_2Cl_2); ^1H NMR (300 MHz, CD_2Cl_2): δ 7.38-7.32 (m, 8H), 7.02 (t, 8H, J = 7.2 Hz), 6.87 (t, 4H, J = 7.2 Hz), 6.48 (s, 1H), 4.38-4.35 (m, 1H), 2.77-2.66 (m, 2H), 2.60-2.51 (m, 1H), 2.10-2.04 (m, 1H), 1.63 (s, 9H), 1.43 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_2$): δ 163.6 (q, J^{13}_{C}-$^{11}_{B}$ = 49.8 Hz), 137.4, 135.6, 125.2 (q, J^{13}_{C}-$^{11}_{B}$ = 2.3 Hz), 121.4, 113.4, 113.4, 63.6, 58.7, 34.7, 28.3, 22.1, 18.5; FABMS [*m/z*(%)] 215 (M–BPh_4, 33), 213 (100), 159 (15), 157 (46); HRMS (FAB) calcd for $C_{11}H_{18}{}^{35}ClN_2$: 213.1159; found 213.1153.

Di-μ-chlorobis[2-[(dimethylamino)methyl]phenyl-C,N]dipalladium(II)[75]

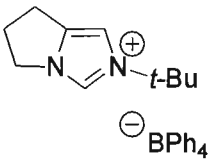


N,N-Dimethyl benzylamine (0.61 mL, 4.0 mmol) in MeOH (20 mL) was treated with palladium dichloride (355 mg, 2.0 mmol), and the mixture was stirred for 4 h. The brown heterogenous mixture turned from green to brown during this period and the mixture was filtered. The collected product was recrystallized from benzene/hexane to give the dimmer complex as yellow crystals (384mg, 70%). mp 183-186 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21-7.14 (m, 2H), 7.00-6.94 (m, 2H), 6.91-6.85 (m, 2H), 3.93 (s, 4H), 2.85 (d, J=8.1 Hz, 12H).

2-*tert*-Butyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-3-ylidene-[2-[(dimethylamino)methyl]phenyl-C,N]palladium(II) chloride (148).



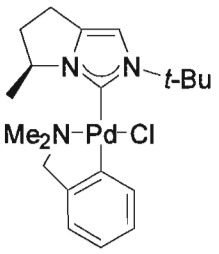
A solution of **143** (103 mg, 0.20 mmol) in THF (10 mL) at –78 °C was treated with *t*-BuLi (0.27 mL, 0.40 mmol) and the reaction mixture was stirred for 1 h. A solution of [(dimethylamino)methyl]phenyl-C,N]palladium(II) chloride dimer (53 mg, 0.10 mmol) in THF (3 mL) was added dropwise to the solution of carbene, and the mixture was allowed to warm slowly to room temperature. The solvent was removed in *vacuo* and column chromatography (silica gel, eluting with ether, then 10% MeOH in CH_2Cl_2) gave **148** (35 mg, 40%) as a light gray solid; mp 221-224 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98-6.88, (m, 2H) 6.81 (s, 1H), 6.71 (td, J = 7.5, 1.2 Hz), 5.93 (d, 1H, J = 7.2 Hz), 4.46-4.40 (m, 1H), 4.15-4.08 (m, 1H), 3.97 (d, 1H, J = 13.8 Hz), 3.76 (d, 1H, J = 13.5 Hz), 2.89 (t, 2H, J = 7.2 Hz), 2.83 (s, 3H). 2.77 (s, 3H), 2.51-2.42 (m, 2H), 1.84 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 161.8, 149.7, 148.2, 135.8, 135.7, 125.3, 123.3, 121.9, 110.9, 72.2, 58.0, 50.9, 49.8, 48.7, 32.0, 27.0, 23.2; FABMS [*m/z*(%)] 439 (M^+, 12), 404 (82), 269 (50), 165 (100), 134 (44), 109 (74); HRMS (FAB) calcd for $C_{19}H_{28}N_3{}^{106}Pd$: 404.1315; found 404.1227.



N.B. Following the same procedure but adding water instead of palladium complex to trap the carbene afforded the dechlorinated imidazolium salt (2-*tert*-Butyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazolium tetraphenylborate) in 50% yield as a colorless solid; ^{1}H NMR (300 MHz, acetone-d_6): δ 8.97 (s, 1H), 7.65 (s, 1H), 7.36-7.31 (m, 8H), 6.92 (t, 8H, J = 7.5 Hz), 6.77 (t, 4H, J = 7.2 Hz), 4.42 (t, 2H, J = 7.2 Hz), 3.08 (t, 2H, J = 7.8 Hz), 2.72 (quin, 2H, J =

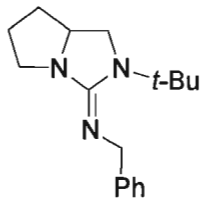
7.5 Hz), 1.72 (s, 9H); FABMS [*m/z*(%)] 165 (M–BPh_4, 100), 109 (21), 57(21), 57(8); HRMS (FAB) calcd for $C_{10}H_{17}N_2$: 165.1392; found 165.1389.

2-*tert*-Butyl-5*S*-methyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-3-ylidene-[2-[(dimethylamino)methyl]phenyl-C,N]palladium(II) chloride (147). A solution of **130**



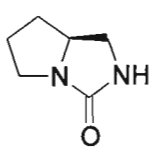
(25 mg, 0.047 mmol) in THF (3 mL) at –78 °C was treated with *t*-BuLi (0.07 mL, 0.09 mmol) and the reaction mixture was stirred for 1 h. A solution of [(dimethylamino)methyl]phenyl-C,N]palladium(II) chloride dimer (13 mg, 0.024 mmol) in THF (1 mL) was added dropwise to the solution of carbene, and the mixture was allowed to warm slowly to room temperature. The solvent was removed in *vacuo* and column chromatography (silica gel, 1:1 EtOAc/hexane) gave **147** (15 mg, 58%), a waxy yellow solid, as a 10:7 mixture of coordination isomers. mp 175-182 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 2 isomers): δ 6.99-6.66 (m, 8H), 6.10 (d, 1H, J = 7.5 Hz), 5.85 (d, 1H, J = 7.2 Hz), 4.88-4.81 (m, 1H), 4.43-4.35 (m, 1H), 4.07 (d, 1H, J = 13.8 Hz), 3.93 (d, 1H, J = 13.8 Hz), 3.83 (d, 1H, J = 13.8 Hz), 3.68 (d, 1H, J = 13.8 Hz), 2.97-2.52 (m, 6H), 2.85 (s, 3H), 2.83 (s, 3H), 2.81 (s, 3H), 2.76 (s, 3H), 2.17-2.08 (m, 2H), 1.95 (d, 3H, J = 6.6 Hz), 1.88 (s, 9H), 1.81 (s, 9H), 1.69 (d. 3H, J = 6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$, 2 isomers): δ 161.4, 161.2, 150.9, 149.5, 148.2, 147.7, 137.3, 135.8, 135.7, 135.6, 125.4, 124.9, 123.3, 123.1, 121.9, 121.7, 110.9, 110.7, 72.3, 58.1, 56.8, 56.2, 51.1, 50.8, 50.3, 49.8, 35.7, 35.4, 32.0 (2C), 21.6, 21.4, 21.1; EIMS [*m/z*(%)] 455 (M^+, 24), 284 (37), 84 (100), 57 (53); HRMS (EI) calcd for $C_{20}H_{30}N_3{}^{35}Cl^{105}Pd$: 452.1174; found 452.1173.

Benzyl-(2-*tert*-butyl-hexahydro-pyrrolo[1,2-c]imidazol-3-ylidene)-amine (*rac*-141)



A solution of racemic urea **105** (67 mg, 0.37 mmol) and $POCl_3$ (0.04 mL, 0.41 mmol) in PhMe (1 mL) was heated at 65 °C for 20 h, and then cooled to rt. CH_2Cl_2 (3 mL) was added and the ice-cooled mixture was treated dropwise with benzylamine (0.16 mL, 1.48 mmol) resulting in the formation of beige precipitates. The reaction mixture was heated at 50 °C for 24 h and cooled to rt. A solution of 1M NaOH (0.37 mL) was added, the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL), and the combined extract was dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography, eluting with 80:18:2 Et_2O-hexane-Et_3N to give colorless solid **147** (37 mg, 37%). mp 52-57 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.41 (m, 2H), 7.30 (t, 2H, J = 7.5 Hz), 7.17 (t, 1H, J = 7.2Hz), 4.56 (q, 2H, J = 20, J = 16 Hz), 3.65-3.62 (m, 1H), 3.44-3.37 (m, 2H), 3.22-3.16 (m, 2H), 1.95-1.86 (m, 2H), 1.80-1.77 (m, 1H), 1.59-1.54 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 159.8, 144.1, 127.8, 127.1, 125.5, 57.2, 53.3, 53.2, 52.3, 47.8, 31.0, 27.6, 27.3, 26.3; EIMS [*m/z*(%)] 271 (M^+, 43), 214 (100), 70 (43).

(–)-Hexahydro-pyrrolo[1,2-c]imidazol-3-one (148)



In a screw-cap vial, urea **105** (47 mg, 0.26 mmol) was treated with TFA (1.5 mL, 6.5 mmol) and thioanisole (0.03 mL, 0.27 mmol). The resulting beige mixture was heated to reflux for 48 h. The reaction was concentrated in *vacuo*, and purified through column chromatography on silica gel eluting with 1:1 EtOAc-hexane; 5% MeOH/CH_2Cl_2 to give a colorless oil (32 mg, 94%). $[\alpha]_D^{20}$ –70 (*c* 0.5, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48 (b, 1H), 3.77-3.56 (m, 1H), 3.65-3.56 (m,

2H), 3.30-3.26 (m, 1H), 3.07-2.98 (m, 1H), 1.99-1.84 (m, 2H), 1.82-1.77 (m, 1H), 1.46-1.39 (m, 1H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 165.8, 59.5, 45.1, 42.9, 30.5, 25.2; EIMS [*m/z*(%)] 126 (M^+, 91), 98 (76), 55 (100).

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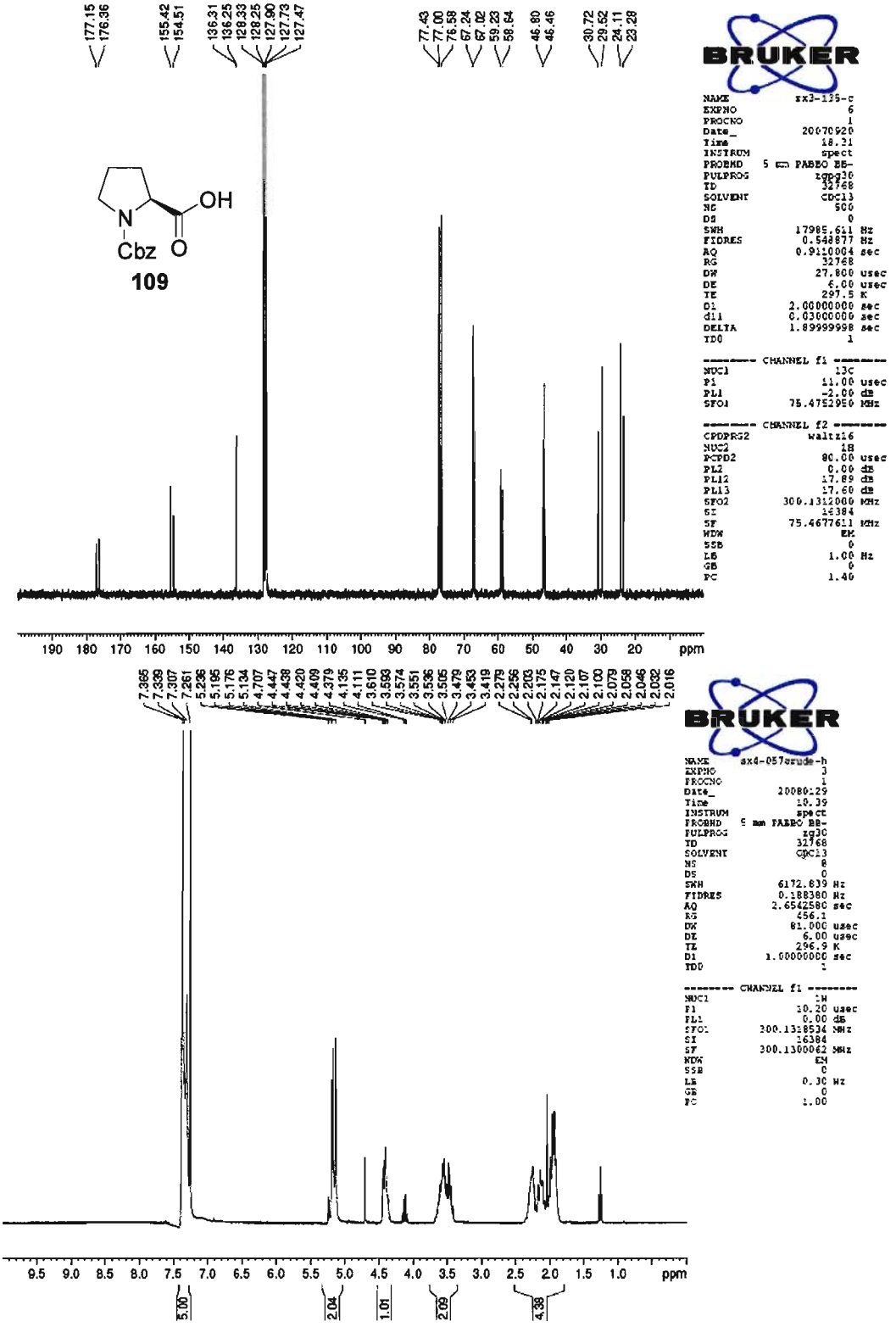
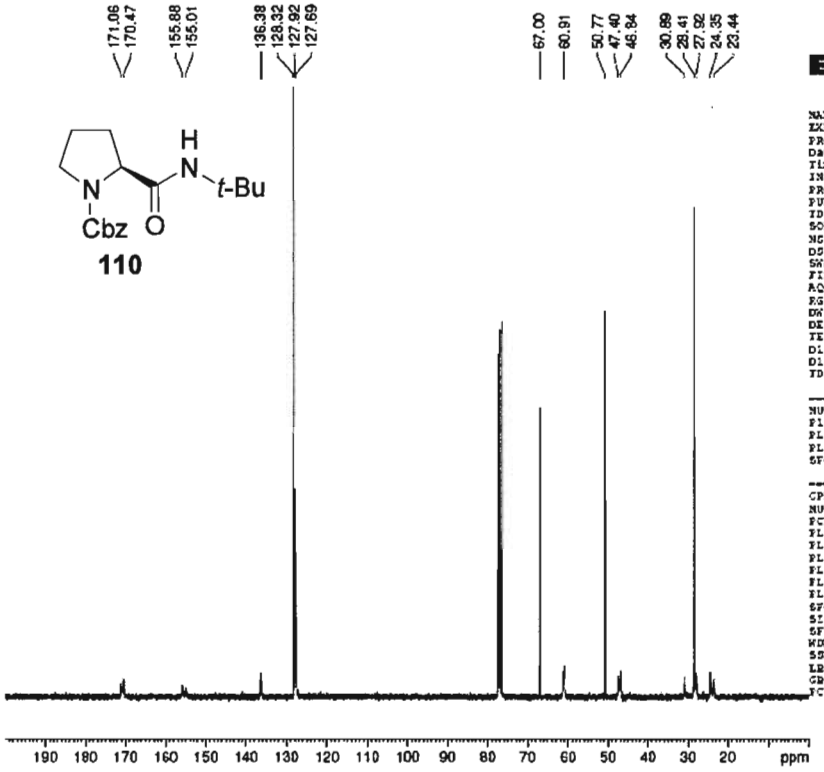
6. Appendix: Spectra






```
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EXPNO                        1
PROCNO                       1
Date_                 20091208
Time                      1.23
INSTRUM                   spect
PROBHD     5 mm PABBO BB-
PULPROG                 zgpg30
TD                       32768
SOLVENT                  CDCl3
NS                         778
DS                           0
SWH                  17985.611 Hz
FIDRES                0.548877 Hz
AQ                    0.9110004 sec
RG                       14596.5
DW                       27.800 usec
DE                        6.00 usec
TE                       296.2 K
D1                    4.00000000 sec
D11                   0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        13C
P1                        11.00 usec
PL1                       -2.00 dB
PL1W                  62.50282669 W
SFO1                  75.4752950 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                     60.00 usec
PL2                        0.00 dB
PL12                      17.89 dB
PL13                      27.60 dB
PL2W                  30.14263725 W
PL12W                 0.48998332 W
PL13W                 0.52381897 W
SFO2                  300.1312000 MHz
SI                         16384
SF                    75.4677611 MHz
WDW                           EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
```

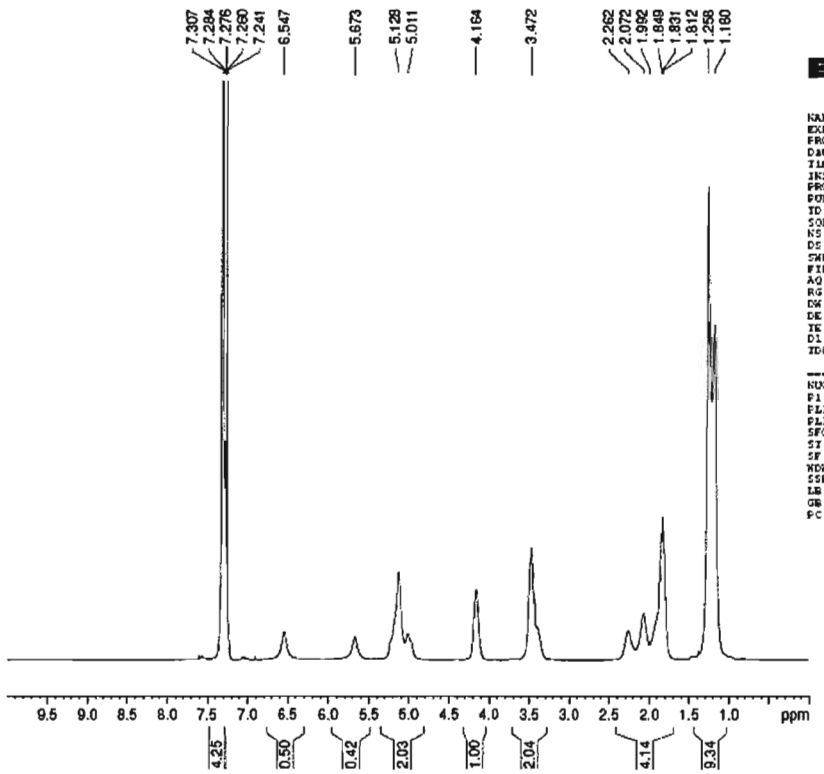


```
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PROCNO                       1
Date_                 20091208
Time                      1.18
INSTRUM                   spect
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                       32768
SOLVENT                  CDCl3
NS                           4
DS                           0
SWH                  6172.839 Hz
FIDRES                0.188383 Hz
AQ                    2.6542580 sec
RG                          32
DW                       81.000 usec
DE                        6.00 usec
TE                       291.5 K
D1                    1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                        1H
P1                        10.20 usec
PL1                        0.00 dB
PL1W                  30.14263725 W
SFO1                  300.1316556 MHz
SI                         16384
SF                    300.1300062 MHz
WDW                           EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00
```
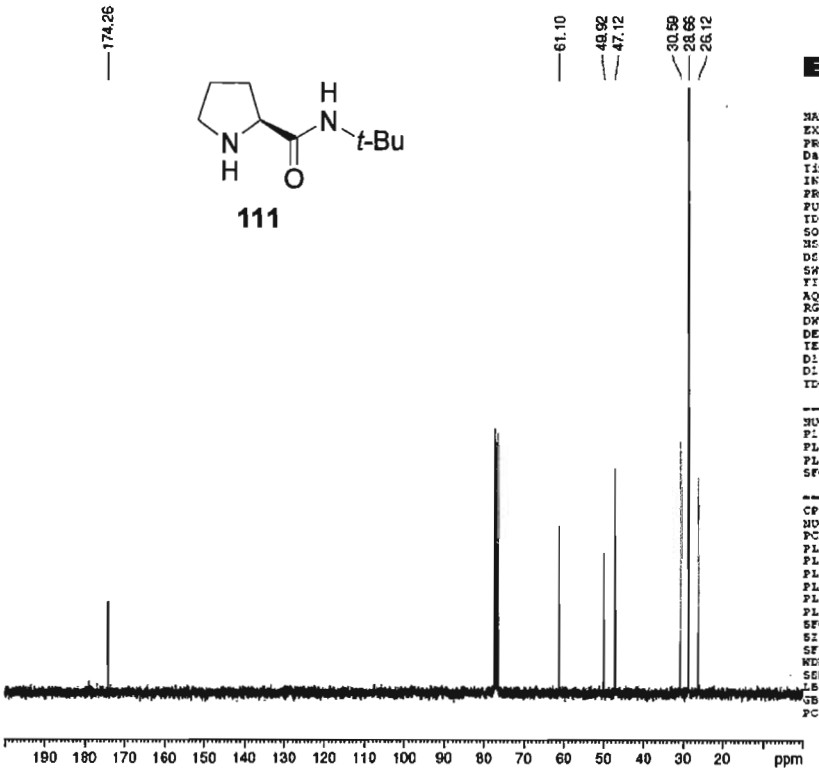
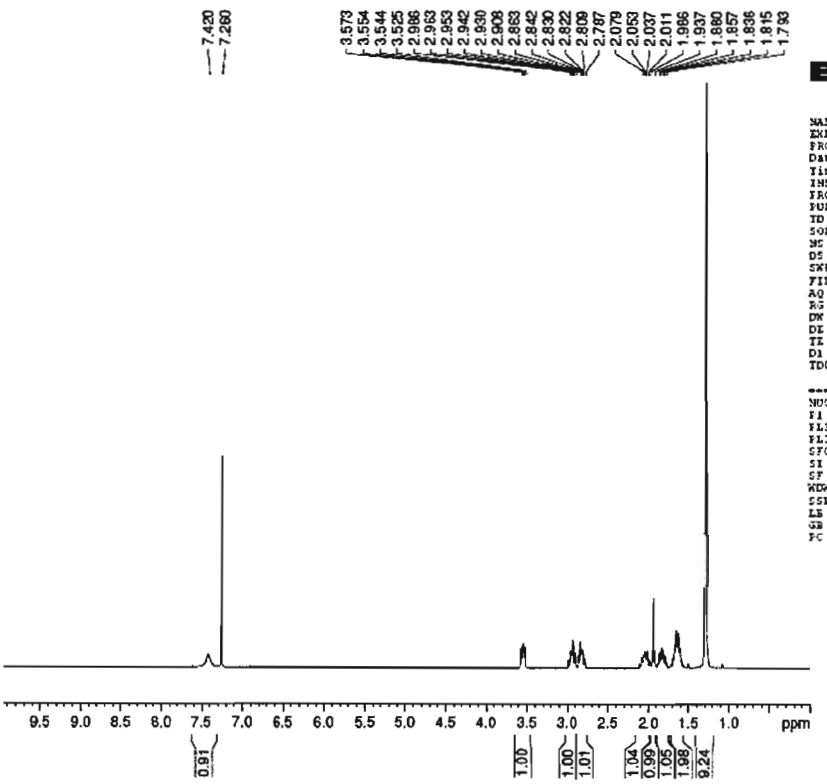
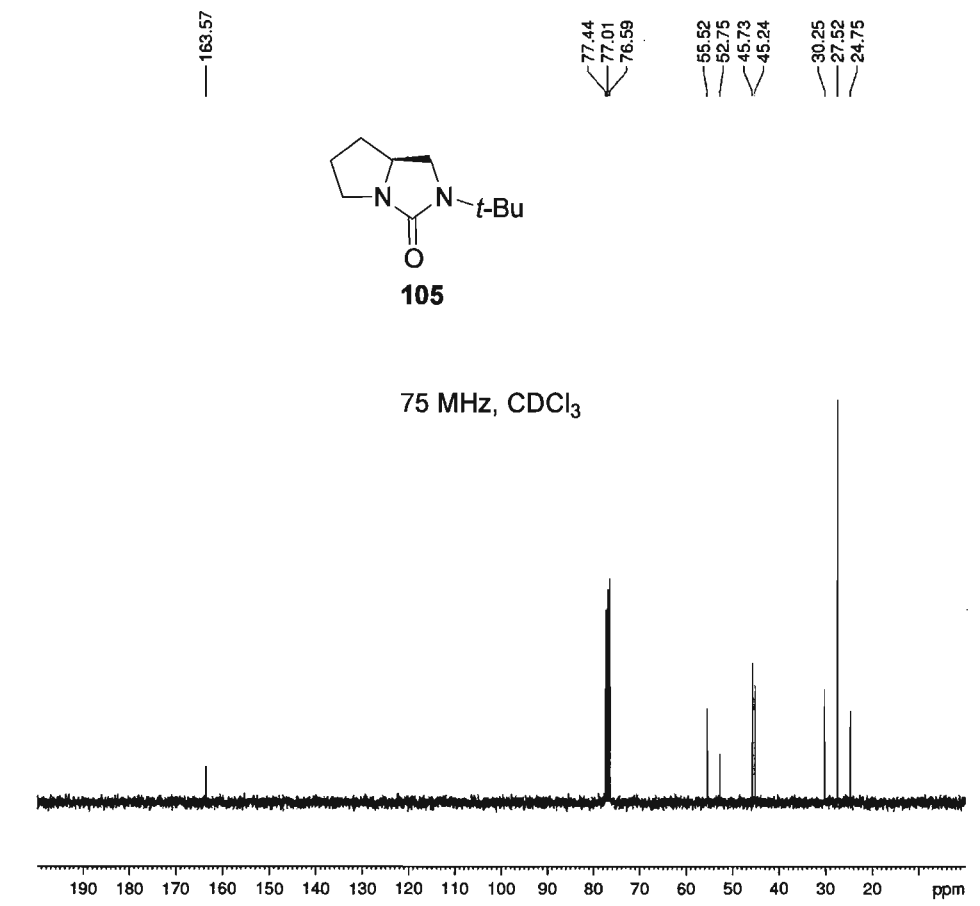
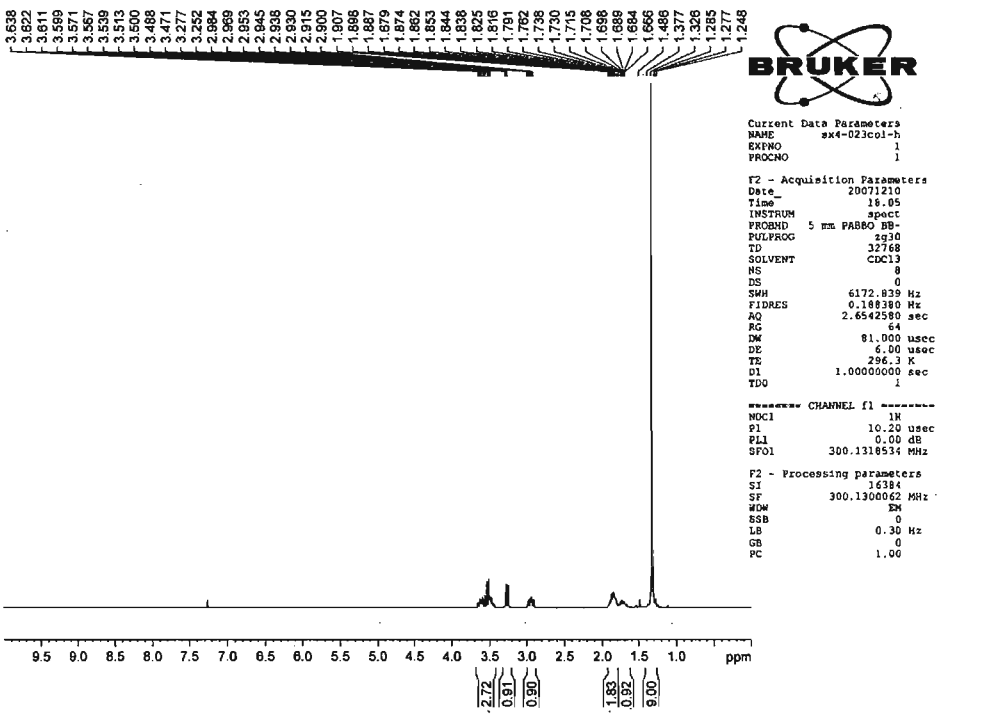


174.26
61.10
48.92
47.12
30.59
28.66
26.12
H
N
N
t-Bu
H
O
111
BRUKER
NAME sx4-077-c
EXPNO 1
PROCNO 1
Date_ 20091208
Time 2.32
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 107
DS 0
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 14596.5
DW 27.800 usec
DE 6.00 usec
TE 296.1 K
D1 4.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 11.00 usec
PL1 -2.00 dB
PL1W 62.50282669 W
SFO1 75.4752950 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 17.89 dB
PL13 17.60 dB
PL2W 30.14263725 W
PL12W 0.48998332 W
PL13W 0.52381897 W
SFO2 300.1312000 MHz
SI 16384
SF 75.4677540 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


7.420
7.260
3.573
3.554
3.544
3.525
2.986
2.963
2.953
2.942
2.930
2.908
2.883
2.842
2.830
2.822
2.809
2.787
2.079
2.053
2.037
2.011
1.986
1.937
1.880
1.857
1.836
1.815
1.793
BRUKER
NAME sx4-077-h
EXPNO 1
PROCNO 1
Date_ 20091208
Time 2.29
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 6172.839 Hz
FIDRES 0.188360 Hz
AQ 2.6542580 sec
RG 64
DW 81.000 usec
DE 6.00 usec
TE 295.9 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PL1W 30.14263725 W
SFO1 300.1318534 MHz
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.91
1.00
1.00
1.01
1.04
0.99
1.05
1.98
9.24


163.57
77.44
77.01
76.59
55.52
52.75
45.73
45.24
30.25
27.52
24.75
N
N
t-Bu
O
105
75 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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PROCNO 1
F2 - Acquisition Parameters
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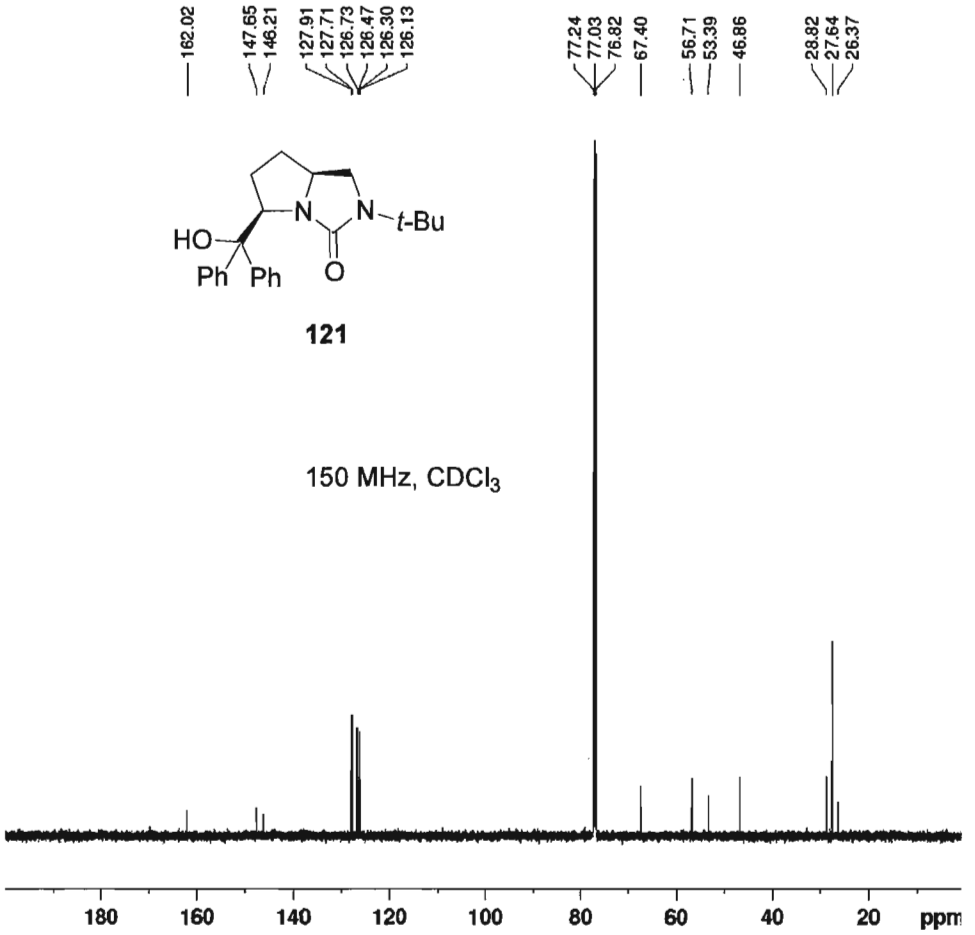
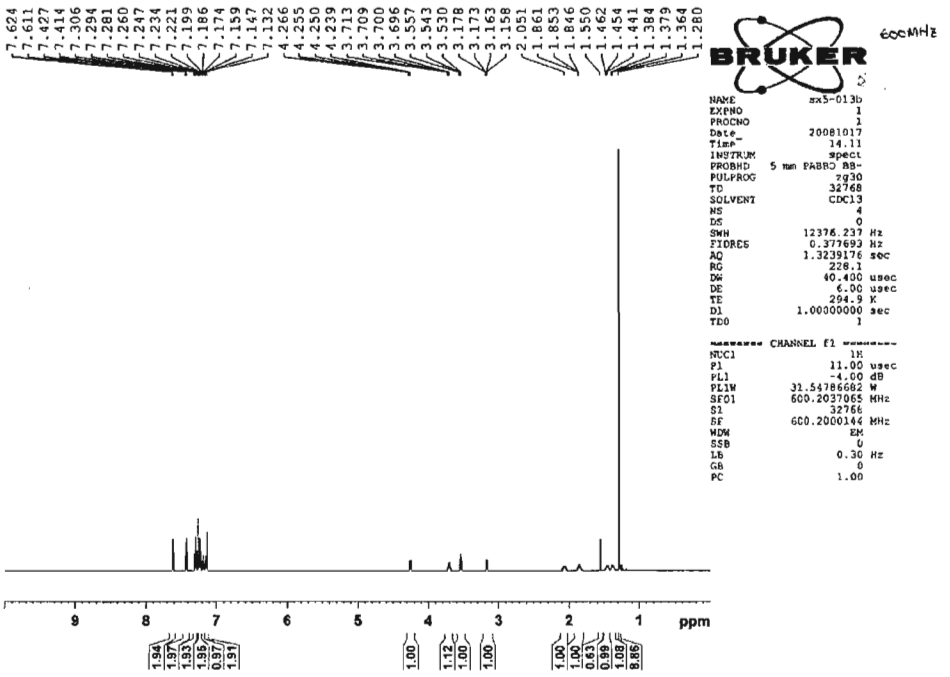
Time 18.05
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 64
DW 81.000 usec
DE 6.00 usec
TE 296.3 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
SFO1 300.1316534 MHz
F2 - Processing parameters
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.72
0.91
0.90
1.83
0.92
9.00


162.02
147.65
146.21
127.91
127.71
126.73
126.47
126.30
126.13
77.24
77.03
76.82
67.40
56.71
53.39
46.86
28.82
27.64
26.37
HO
Ph
Ph
N
N
t-Bu
O
121
150 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm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7.611
7.427
7.414
7.306
7.294
7.281
7.260
7.247
7.234
7.221
7.199
7.186
7.174
7.159
7.147
7.132
4.266
4.255
4.250
4.239
3.713
3.709
3.700
3.696
3.557
3.543
3.530
3.178
3.173
3.163
3.158
2.051
1.861
1.853
1.846
1.550
1.462
1.454
1.441
1.384
1.379
1.364
1.280
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600MHz
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EXPNO 1
PROCNO 1
Date_ 20081017
Time_ 14.11
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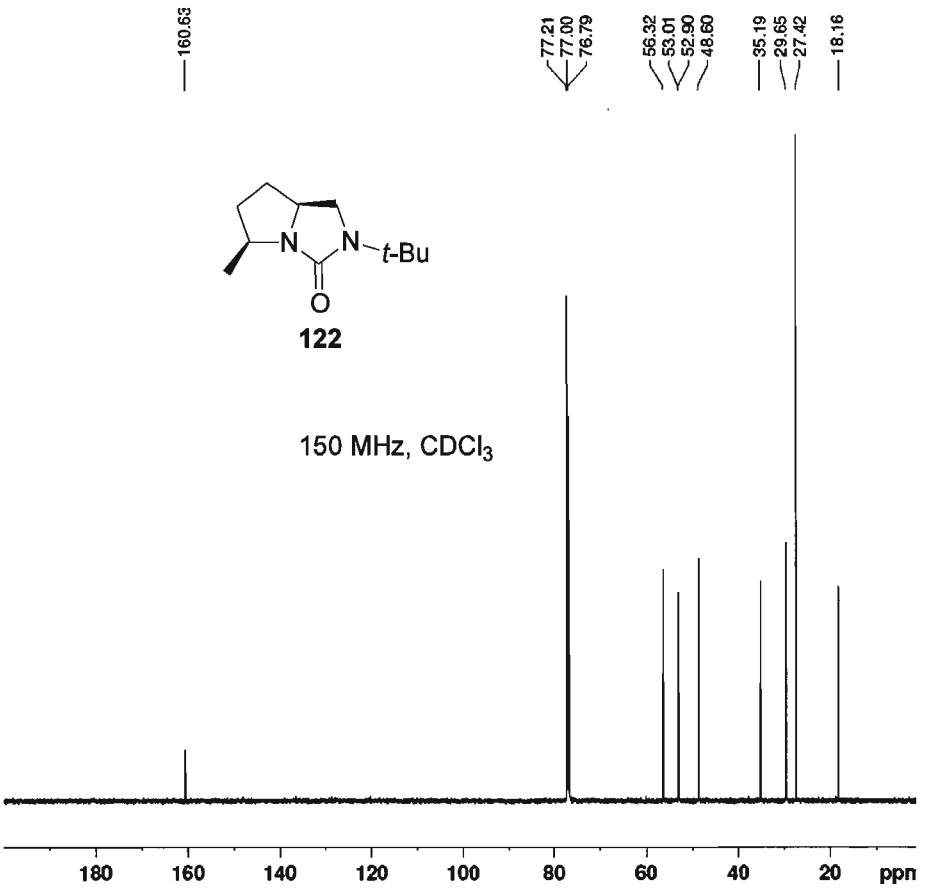
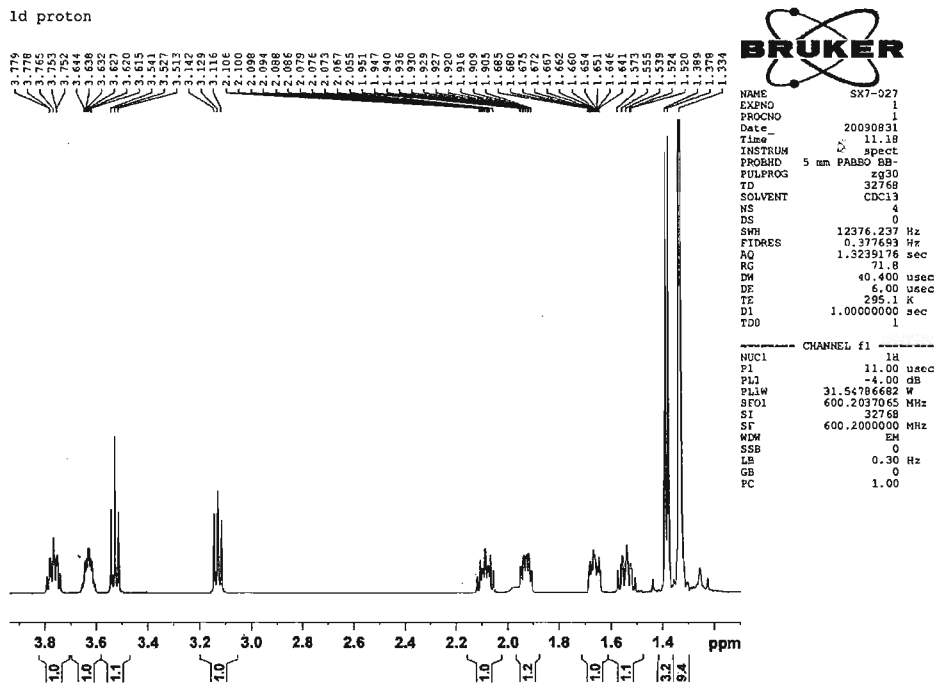
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 12376.237 Hz
FIDRES 0.377693 Hz
AQ 1.3239176 sec
RG 228.1
DW 40.400 usec
DE 6.00 usec
TE 294.9 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.00 usec
PL1 -4.00 dB
PL1W 31.54786682 W
SFO1 600.2037065 MHz
SI 32768
SF 600.2000144 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
1.94
1.97
1.93
1.95
0.97
1.91
1.00
1.12
1.00
1.00
1.00
1.00
0.63
0.99
1.08
8.86


160.63
77.21
77.00
76.79
56.32
53.01
52.90
48.60
35.19
29.65
27.42
18.16
N
N
t-Bu
O
122
150 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm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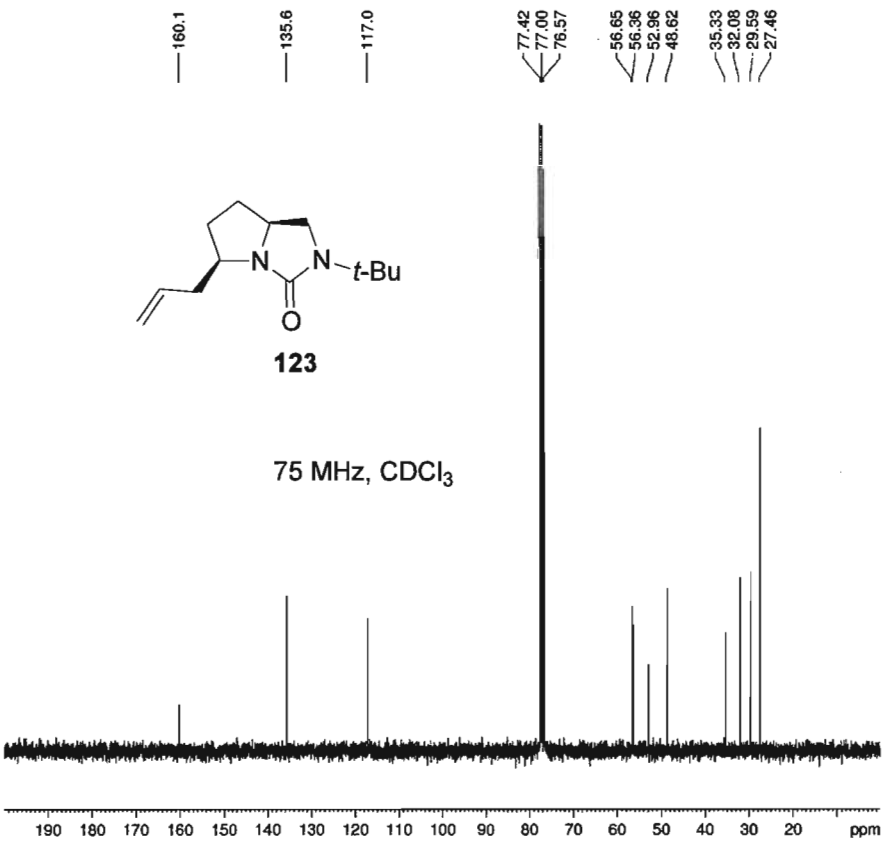
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 12376.237 Hz
FIDRES 0.377693 Hz
AQ 1.3239176 sec
RG 71.8
DW 40.400 usec
DE 6.00 usec
TE 295.1 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1d
P1 11.00 usec
PL1 -4.00 dB
PL1W 31.54786682 W
SFO1 600.2037065 MHz
SI 32768
SF 600.2000000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
ppm
1.0
1.0
1.1
1.0
1.0
1.2
1.0
1.1
3.2
9.4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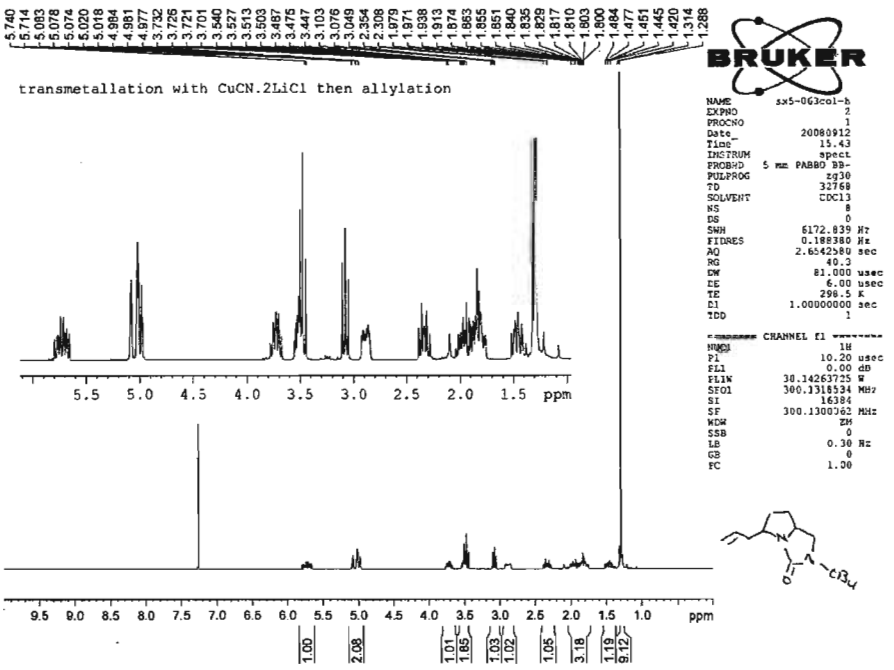
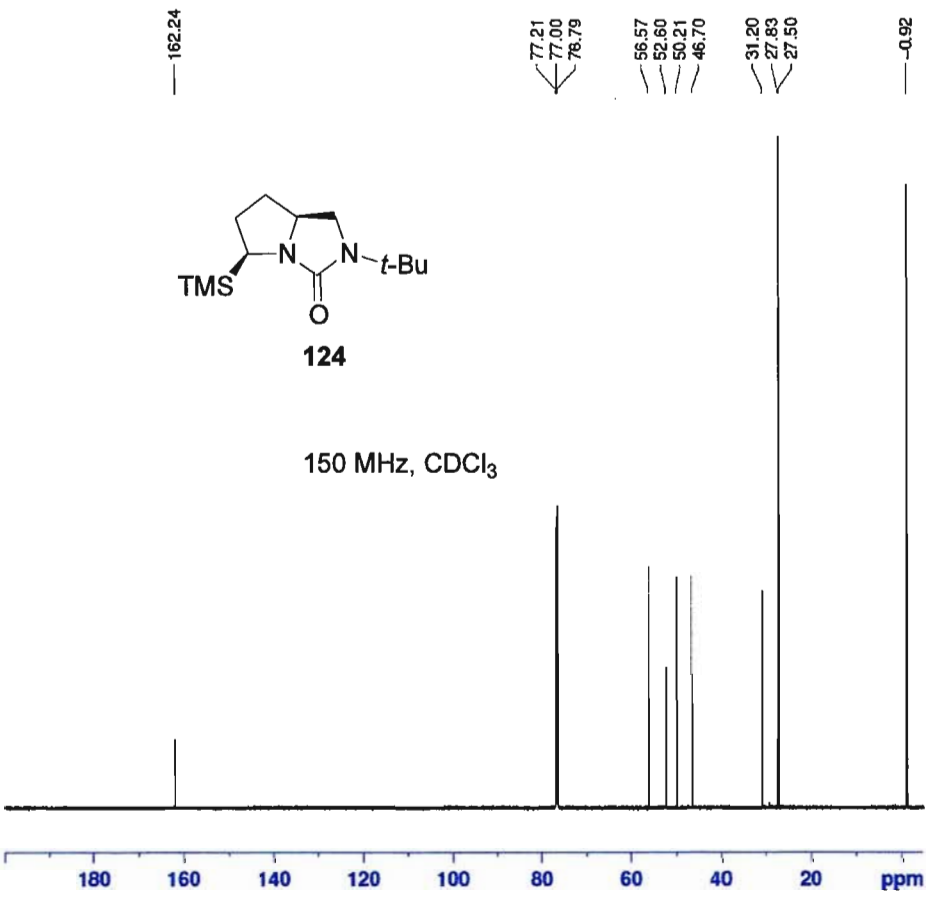
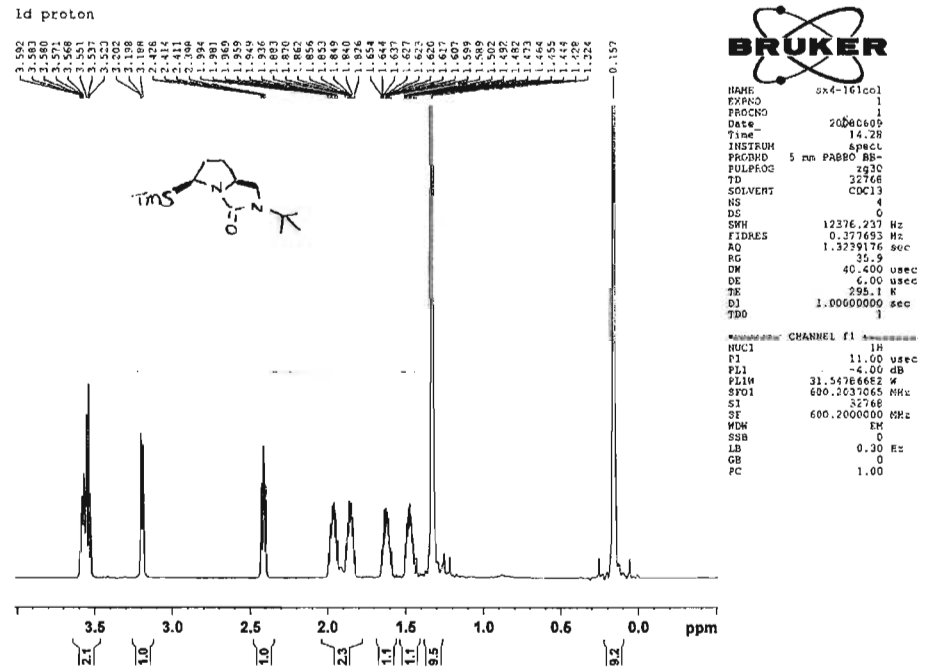
135.6
117.0
77.42
77.00
76.57
56.65
56.36
52.96
48.62
35.33
32.08
29.59
27.46
N
N
t-Bu
O
123
75 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


transmetallation with CuCN.2LiCl then allylation
BRUKER
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.08
1.01
1.85
1.03
1.02
1.05
3.18
1.19
9.12


162.24
77.21
77.00
76.79
56.57
52.60
50.21
46.70
31.20
27.83
27.50
-0.92
TMS
N
N
t-Bu
O
124
150 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm


1d proton
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PROCNO 1
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Time 14.28
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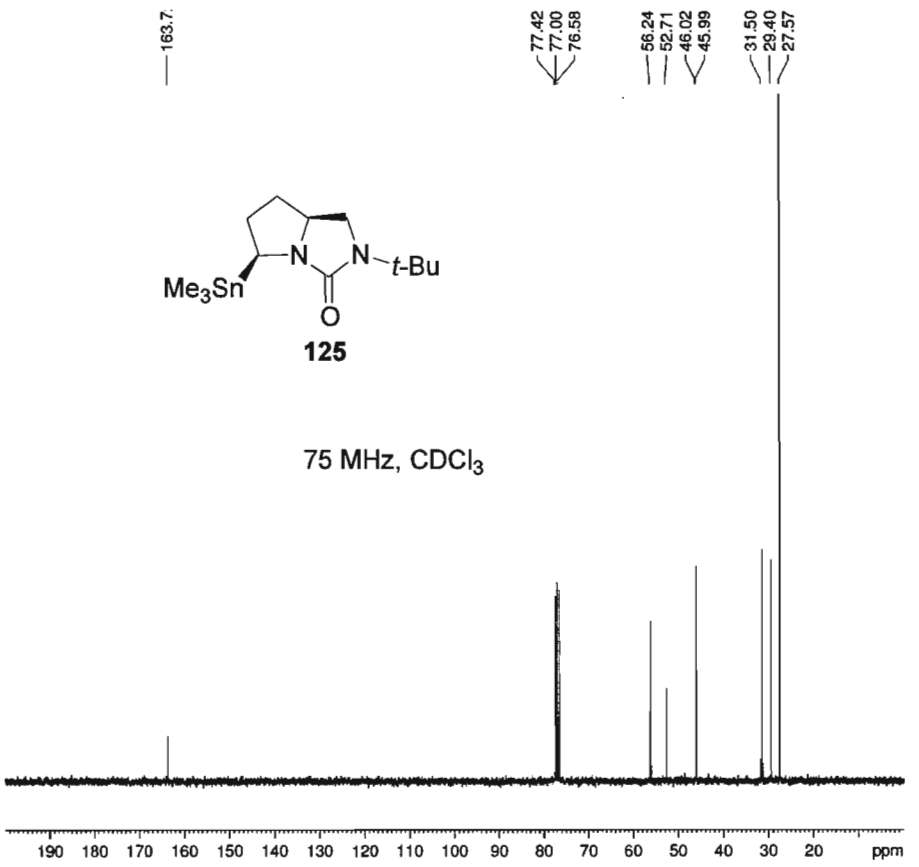
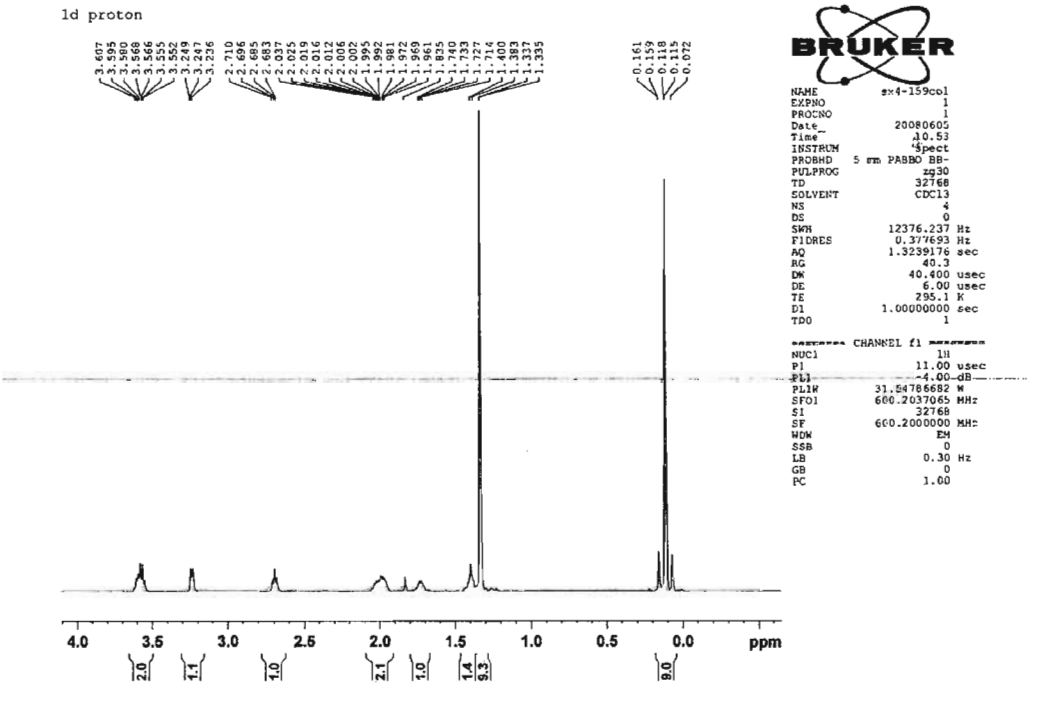
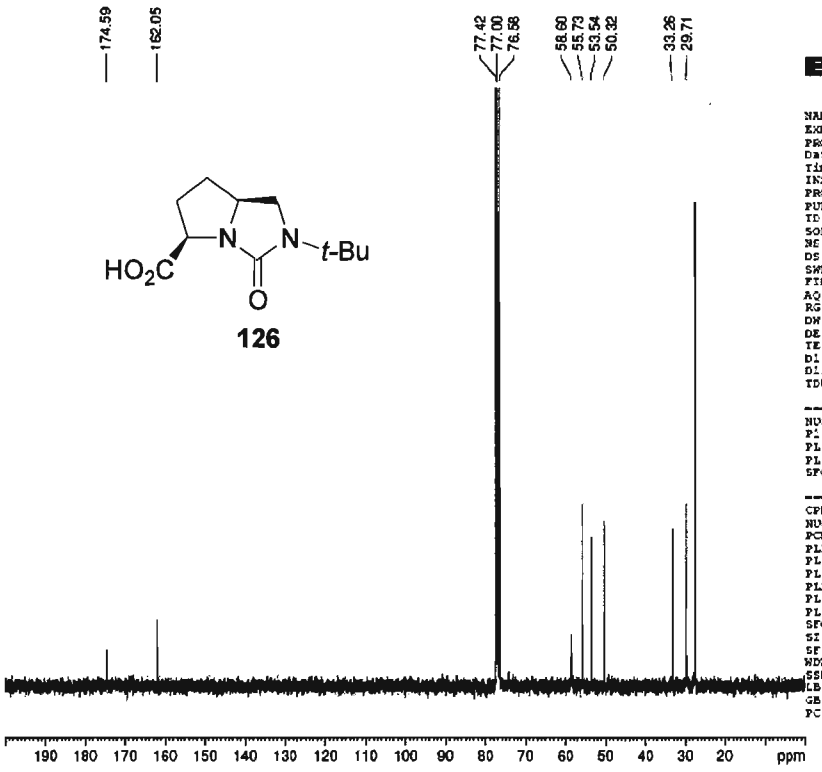
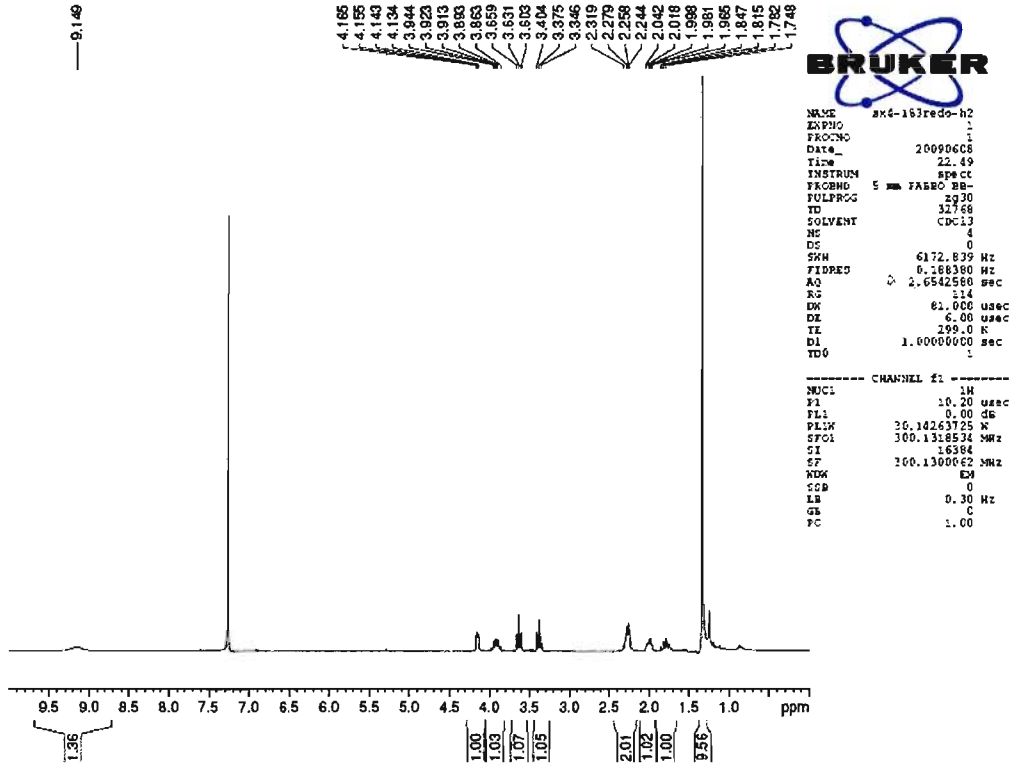
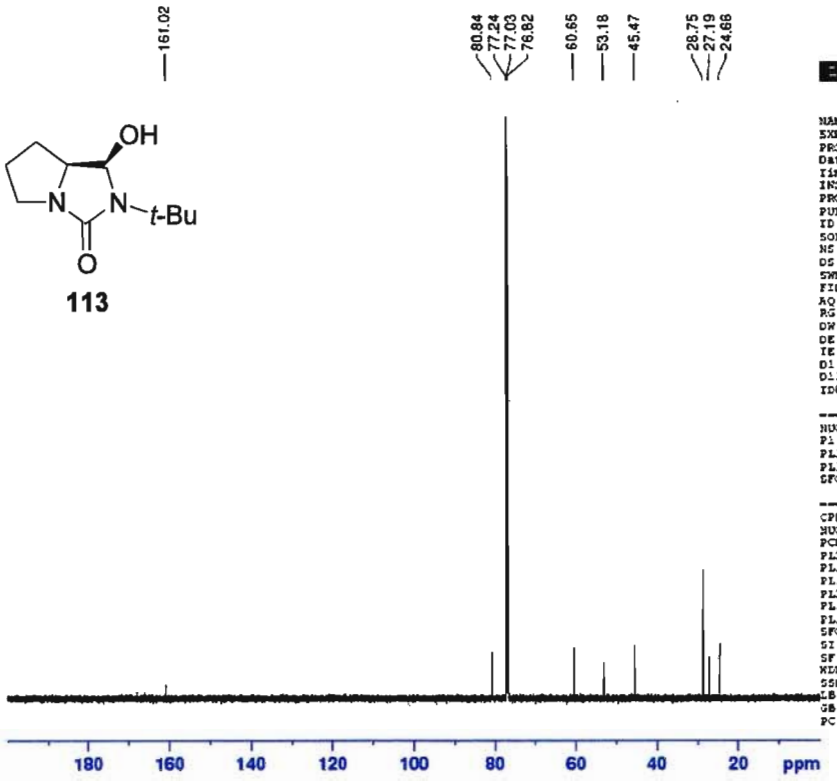
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 12376.237 Hz
FIDRES 0.377693 Hz
AQ 1.3239176 sec
RG 35.9
DW 40.400 usec
DE 6.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.00 usec
PL1 -4.00 dB
PL1W 31.54786682 W
SFO1 600.2037065 MHz
SI 32768
SF 600.2000000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
TMS
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.1
1.0
1.0
2.3
1.1
1.1
9.5
9.2


163.7
77.42
77.00
76.58
56.24
52.71
46.02
45.99
31.50
29.40
27.57
Me3Sn
N
N
t-Bu
O
125
75 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


1d proton
3.607
3.595
3.580
3.568
3.555
3.552
3.249
3.247
3.236
2.710
2.696
2.685
2.683
2.037
2.025
2.016
2.012
2.006
2.002
1.995
1.992
1.981
1.972
1.968
1.961
1.835
1.740
1.733
1.727
1.714
1.400
1.383
1.337
1.335
0.161
0.159
0.118
0.115
0.072
BRUKER
NAME ex4-159col
EXPNO 1
PROCNO 1
Date_ 20080605
Time 10.53
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 12376.237 Hz
FIDRES 0.377693 Hz
AQ 1.3239176 sec
RG 40.3
DW 40.400 usec
DE 6.00 usec
TE 295.1 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.00 usec
PL1 -4.00 dB
PL1W 31.54786682 W
SFO1 600.2037065 MHz
SI 32768
SF 600.2000000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.0
1.1
1.0
2.1
1.0
1.4
9.3
9.0

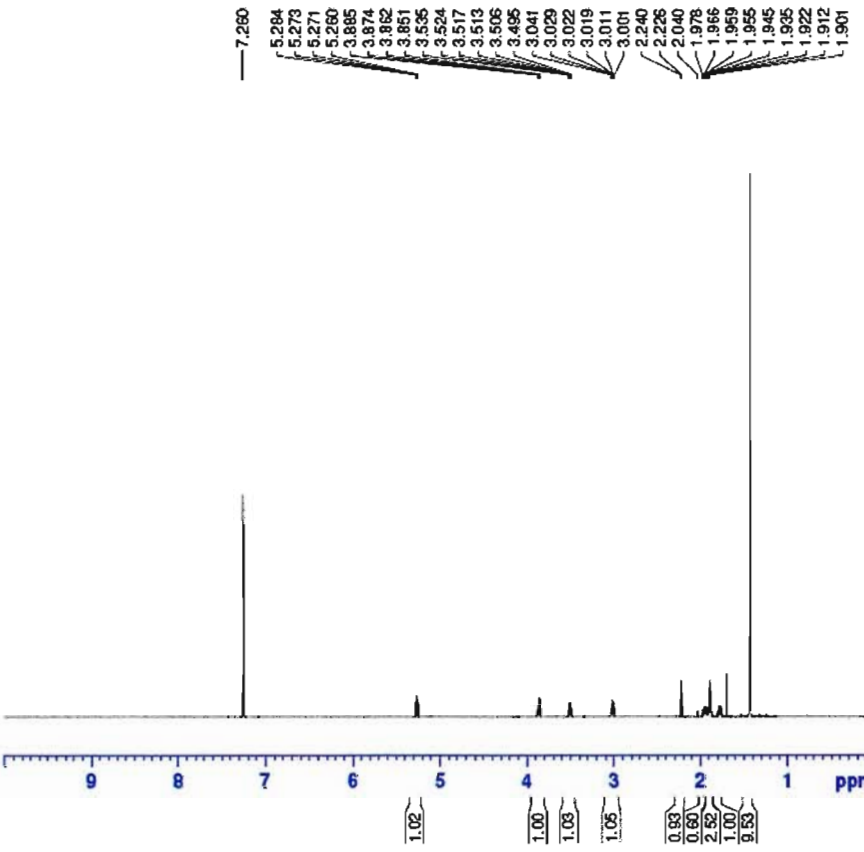

174.59
162.05
77.42
77.00
76.58
58.60
55.73
53.54
50.32
33.26
29.71
HO2C
N
N
t-Bu
O
126
BRUKER
NAME sx4-183-c
EXPNO 1
PROCNO 1
Date_ 20090608
Time 22.18
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 256
DS 0
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 299.2 K
D1 4.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 11.00 usec
PL1 -2.00 dB
PL1W 62.50282669 W
SFO1 75.4752950 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 17.89 dB
PL13 17.60 dB
PL2W 30.14263725 W
PL12W 0.48998322 W
PL13W 0.52381897 W
SFO2 300.1312000 MHz
SI 16384
SF 75.4677515 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


9.149
4.165
4.155
4.143
4.134
3.944
3.923
3.913
3.893
3.863
3.659
3.631
3.603
3.404
3.375
3.346
2.319
2.279
2.258
2.244
2.042
2.018
1.998
1.981
1.965
1.847
1.815
1.782
1.748
BRUKER
NAME sx4-183redo-h2
EXPNO 1
PROCNO 1
Date_ 20090608
Time 22.49
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 114
DW 81.000 usec
DE 6.00 usec
TE 299.0 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PL1W 30.14263725 W
SFO1 300.1318534 MHz
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.36
1.00
1.03
1.07
1.05
2.01
1.02
1.00
9.56



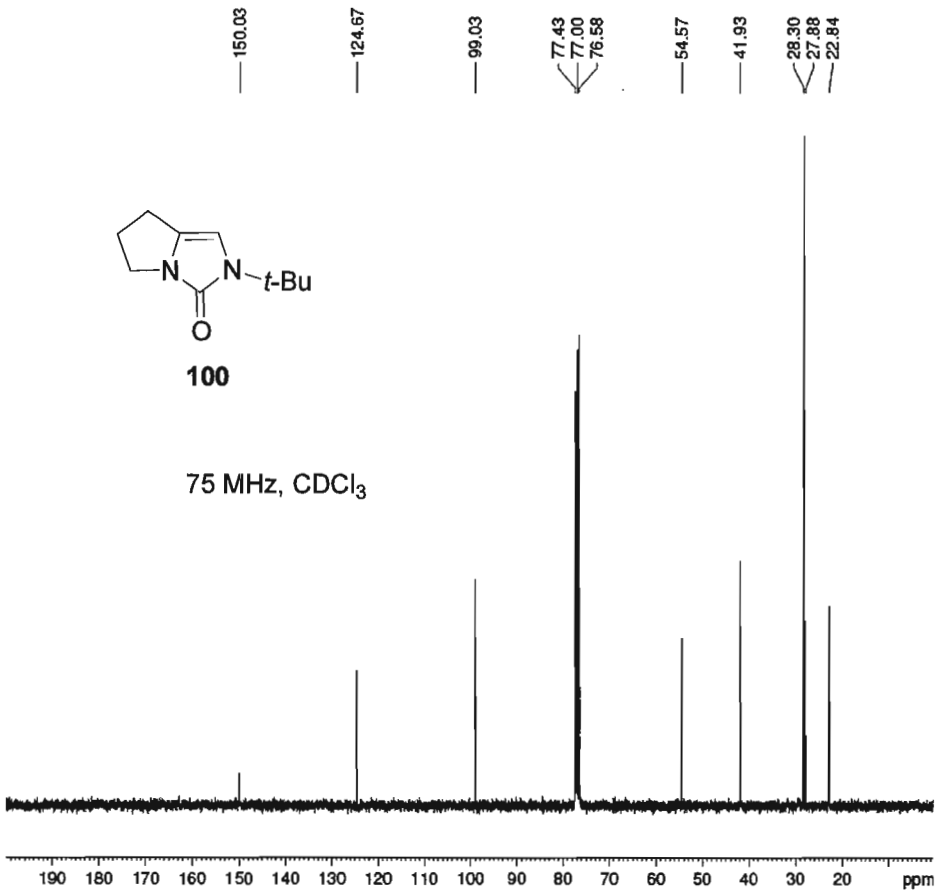
BRUKER

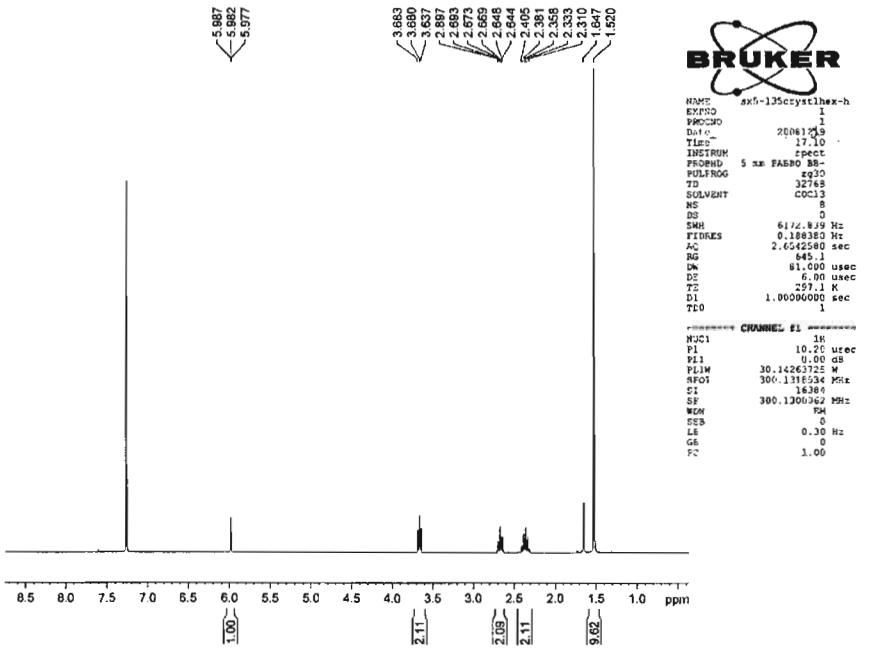
```
NAME          SX5-145cryst1
EXPNO                     2
PROCNO                    1
Date_              20090123
Time                  13.19
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG               zgpg30
TD                     32768
SOLVENT               CDCl3
NS                      256
DS                        0
SWH               35971.223 Hz
FIDRES             1.097755 Hz
AQ                0.4555391 sec
RG                  20642.5
DW                   13.900 usec
DE                    6.00 usec
TE                   295.5 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     13C
P1                      8.00 usec
PL1                    -1.00 dB
PL1W            92.33850861 W
SFO1           150.9355021 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                     1H
PCPD2                 70.00 usec
PL2                   -4.00 dB
PL12                  12.07 dB
PL13                  15.00 dB
PL2W            31.54786682 W
PL12W           0.77977633 W
PL13W           0.39716411 W
SFO2           600.2024008 MHz
SI                     32768
SF             150.9204100 MHz
WDW                       EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

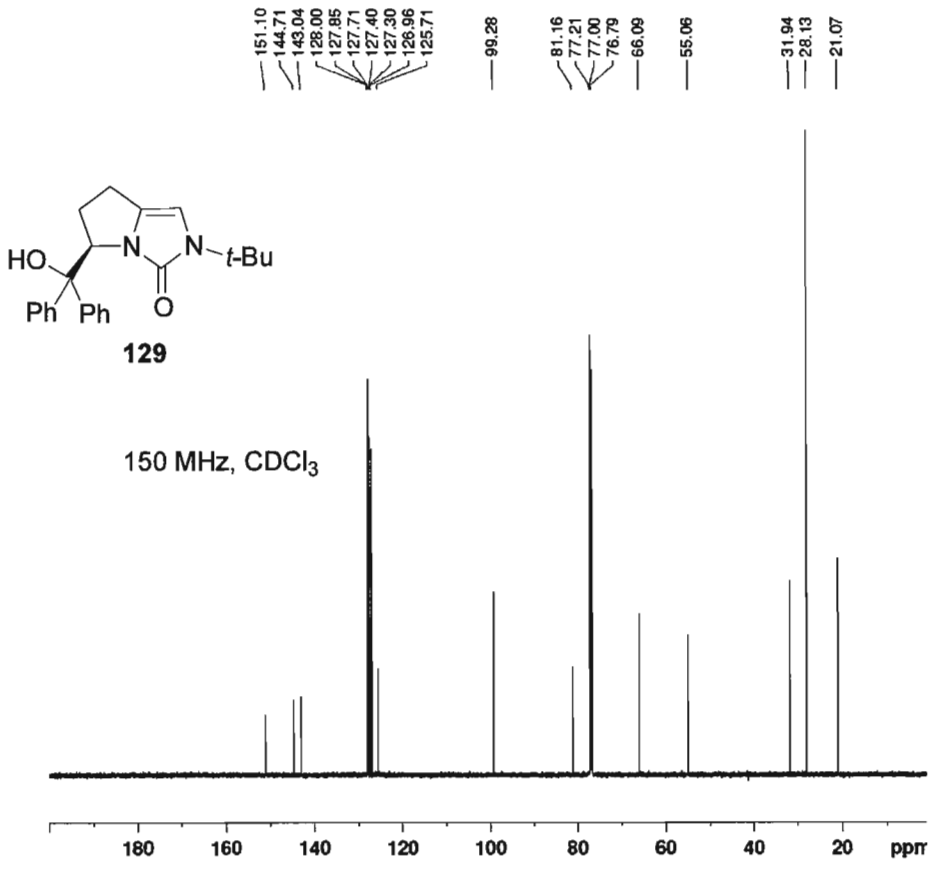


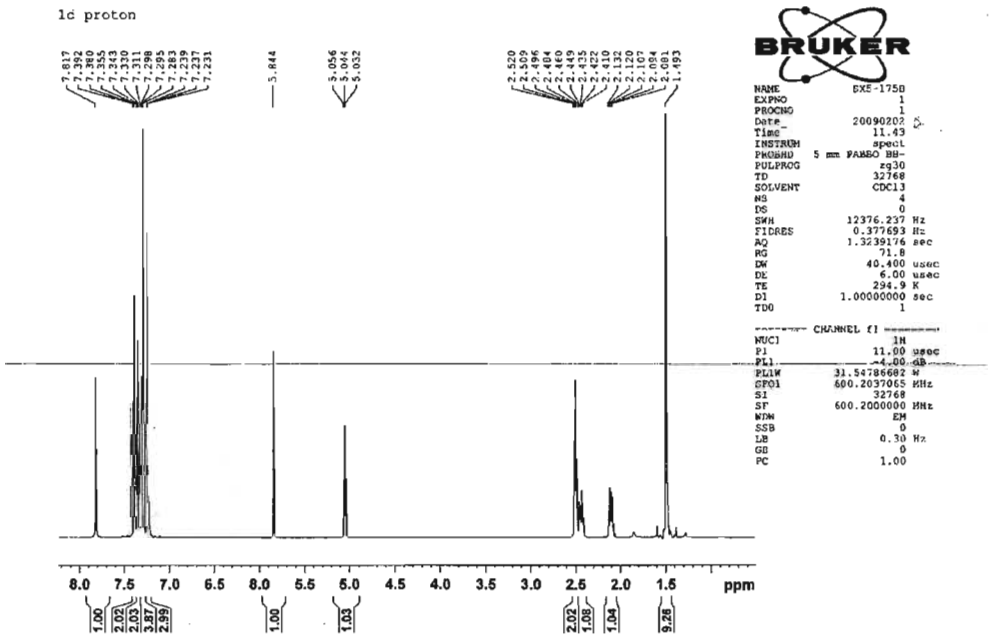
BRUKER

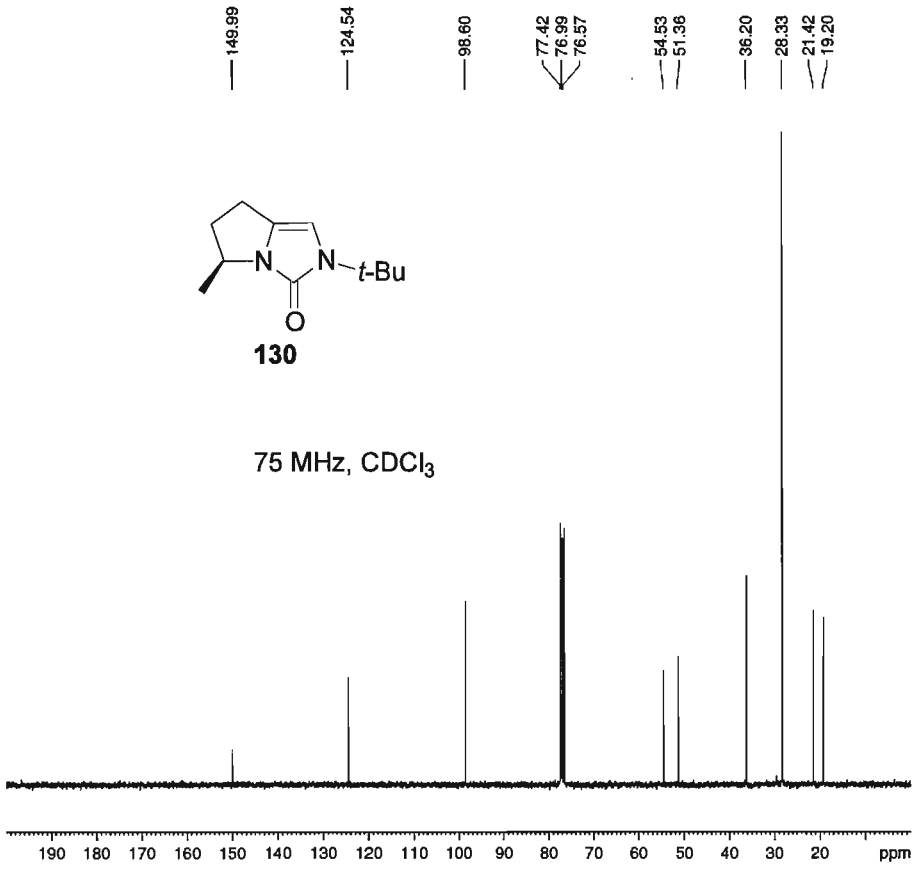
```
NAME          SX5-145cryst1
EXPNO                     1
PROCNO                    1
Date_              20090123
Time                  13.14
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                     32768
SOLVENT               CDCl3
NS                        4
DS                        0
SWH               12376.237 Hz
FIDRES             0.377693 Hz
AQ                1.3239176 sec
RG                      128
DW                   40.400 usec
DE                    6.00 usec
TE                   295.1 K
D1                1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                     11.00 usec
PL1                    -4.00 dB
PL1W            31.54786682 W
SFO1           600.2037065 MHz
SI                     32768
SF             600.2000140 MHz
WDW                       EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

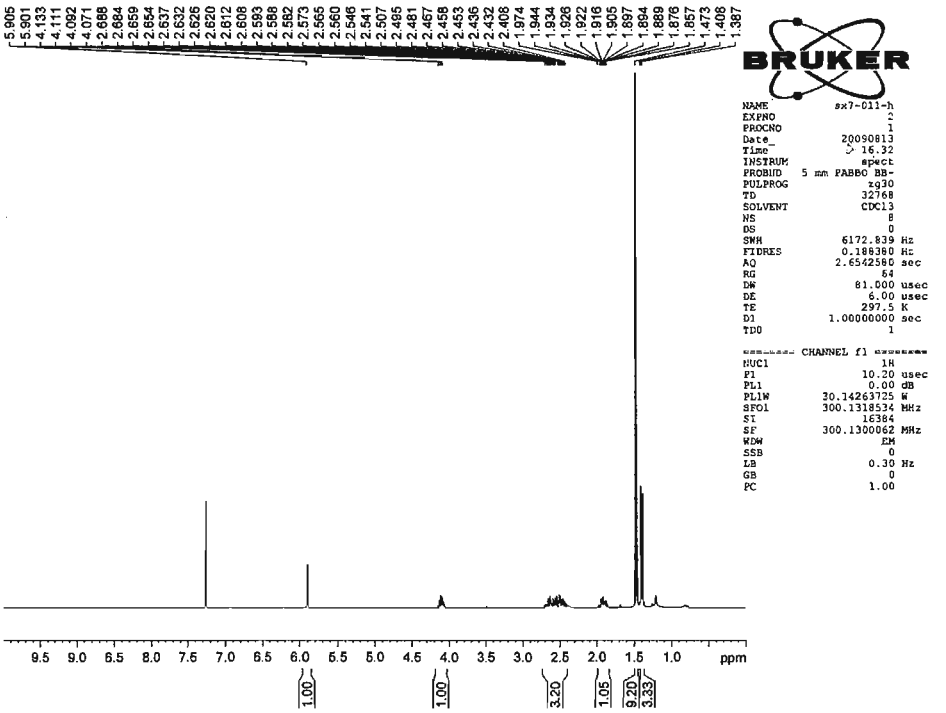

150.03
124.67
99.03
77.43
77.00
76.58
54.57
41.93
28.30
27.88
22.84
N
N
t-Bu
O
100
75 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

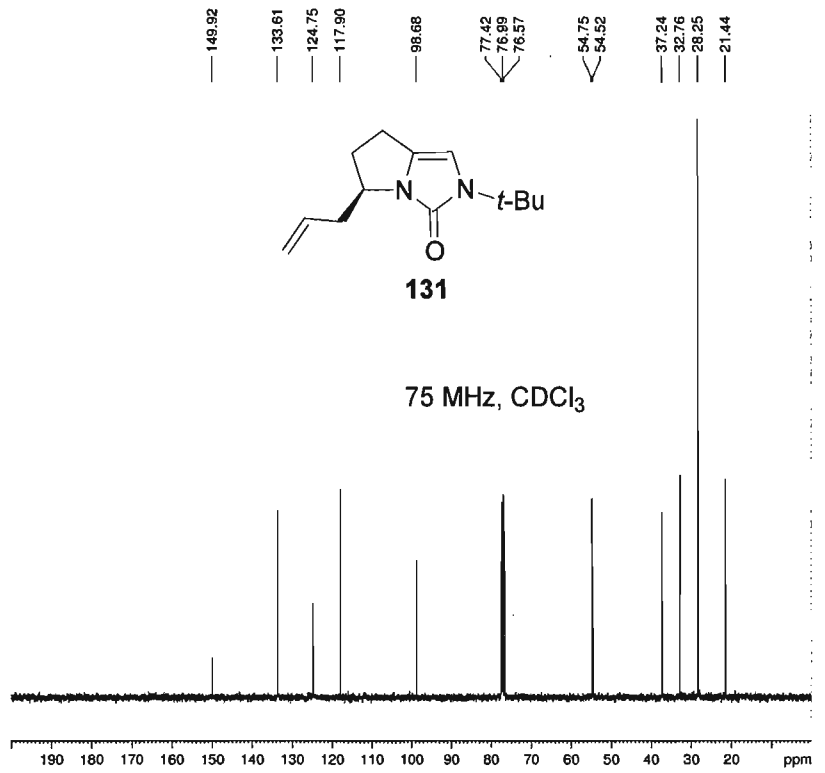

5.987
5.982
5.977
3.683
3.680
3.637
2.897
2.683
2.673
2.669
2.648
2.644
2.405
2.381
2.358
2.333
2.310
1.647
1.520
BRUKER
NAME sx5-135crystlhex-h
EXPNO 1
PROCNO 1
Date_ 20061219
TIME 17.10
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 6172.839 Hz
FIDRES 0.188383 Hz
AQ 2.6542580 sec
RG 645.1
DW 81.000 usec
DE 6.00 usec
TE 297.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PLW 30.14263725 W
SFO1 300.1318534 MHz
SI 16384
SF 300.1300962 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.11
2.09
2.11
9.62

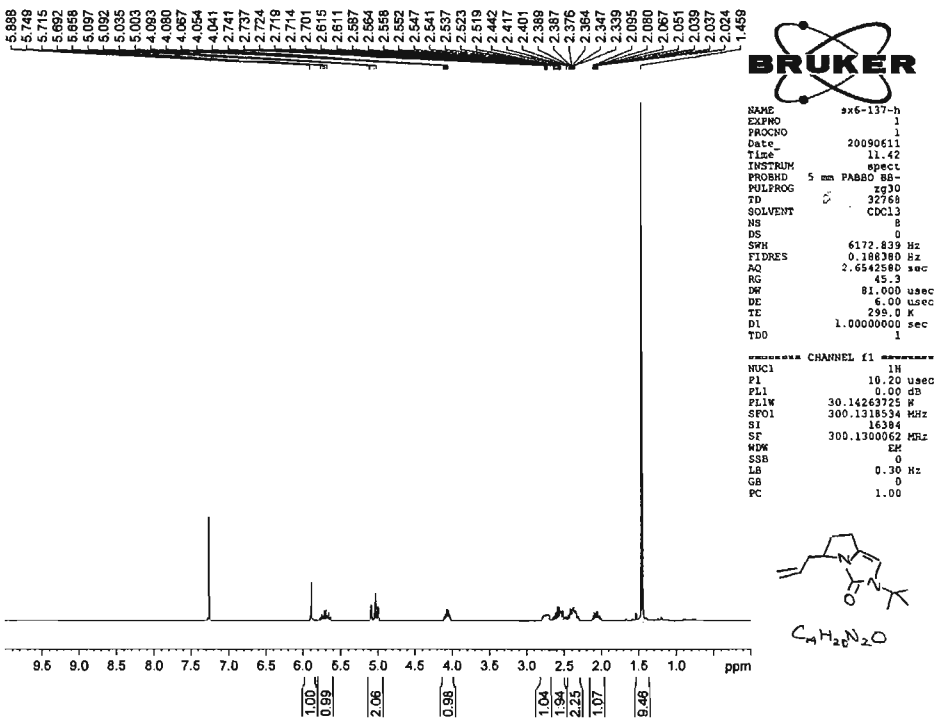

151.10
144.71
143.04
128.00
127.85
127.71
127.40
127.30
126.96
125.71
99.28
81.16
77.21
77.00
76.79
66.09
55.06
31.94
28.13
21.07
HO
Ph
Ph
N
N
t-Bu
O
129
150 MHz, CDCl3
180
160
140
120
100
80
60
40
20
ppm

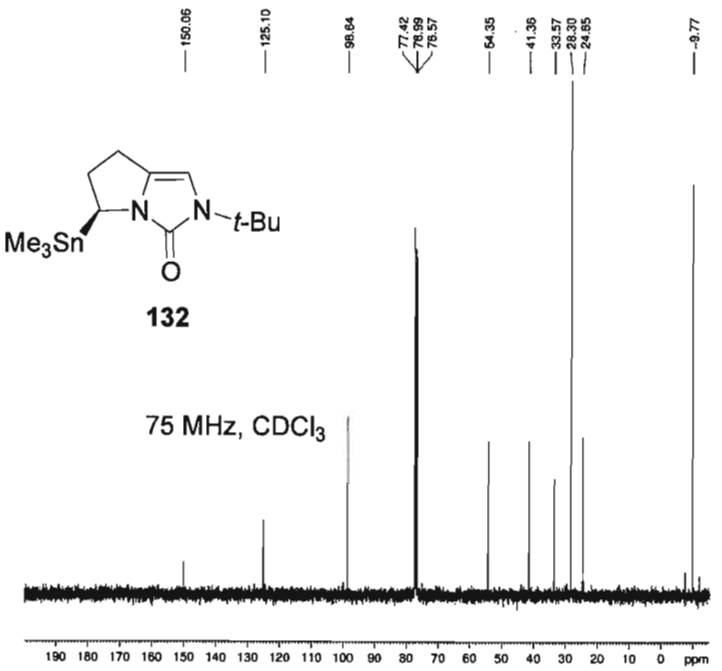

1d proton
7.817
7.392
7.380
7.355
7.343
7.310
7.311
7.298
7.295
7.283
7.239
7.237
7.231
5.844
5.056
5.044
5.032
2.520
2.509
2.496
2.484
2.460
2.445
2.435
2.422
2.410
2.132
2.120
2.107
2.094
2.081
1.493
BRUKER
NAME EXE-175B
EXPNO 1
PROCNO 1
Date 20090202
Time 11.43
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 12376.237 Hz
FIDRES 0.377693 Hz
AQ 1.3239176 sec
RG 71.8
DW 40.400 usec
DE 6.00 usec
TE 294.9 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.00 usec
PL1 -4.00 dB
PL1W 31.54786682 W
SFO1 600.2037065 MHz
SI 32768
SF 600.2000000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
2.02
2.03
3.87
2.96
1.00
1.03
2.02
1.08
1.04
9.26

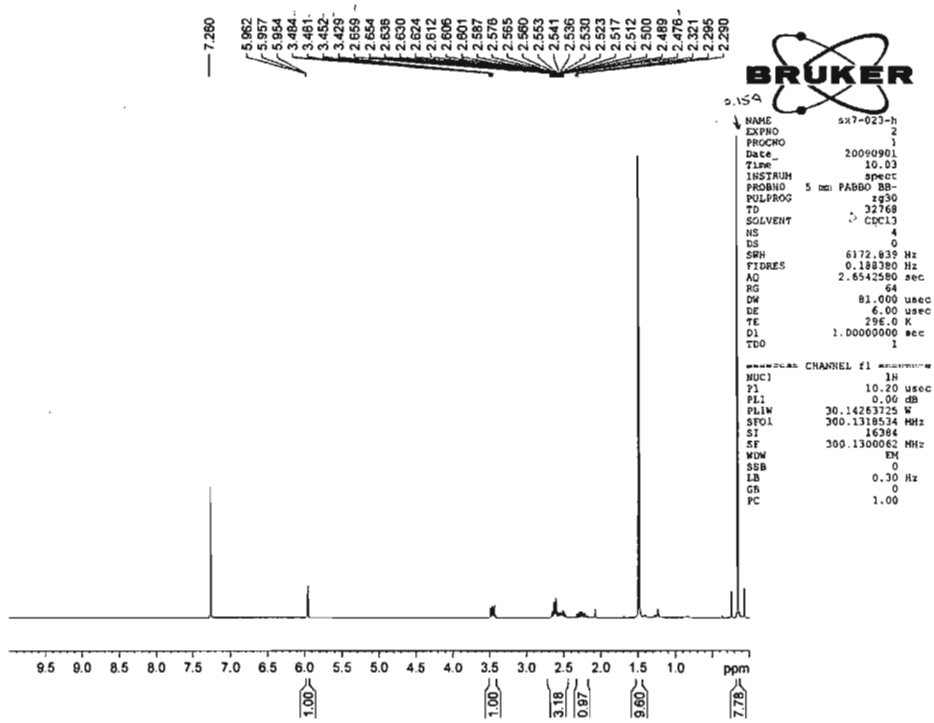

149.99
124.54
98.60
77.42
76.99
76.57
54.53
51.36
36.20
28.33
21.42
19.20
N
N
t-Bu
O
130
75 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

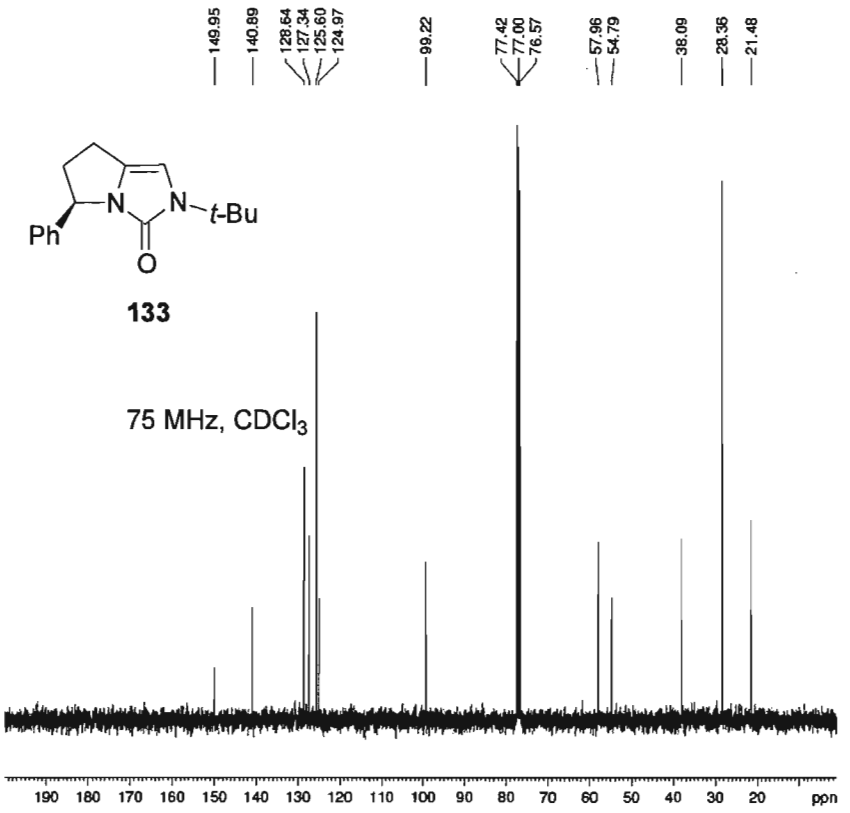

5.905
5.901
4.133
4.111
4.092
4.071
2.888
2.884
2.859
2.854
2.637
2.632
2.626
2.620
2.612
2.608
2.593
2.588
2.582
2.573
2.565
2.560
2.546
2.541
2.507
2.495
2.481
2.467
2.458
2.453
2.436
2.432
2.408
1.974
1.944
1.934
1.926
1.922
1.916
1.905
1.897
1.894
1.889
1.878
1.857
1.473
1.408
1.387
BRUKER
NAME sx7-011-h
EXPNO 2
PROCNO 1
Date_ 20090813
Time 16.32
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 6172.839 Hz
FIDRES 0.188360 Hz
AQ 2.6542580 sec
RG 64
DW 81.000 usec
DE 6.00 usec
TE 297.5 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PL1W 30.14263725 W
SFO1 300.1318534 MHz
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
3.20
1.05
9.20
3.33


149.92
133.61
124.75
117.90
98.68
77.42
76.99
76.57
54.75
54.52
37.24
32.76
28.25
21.44
N
N
t-Bu
O
131
75 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

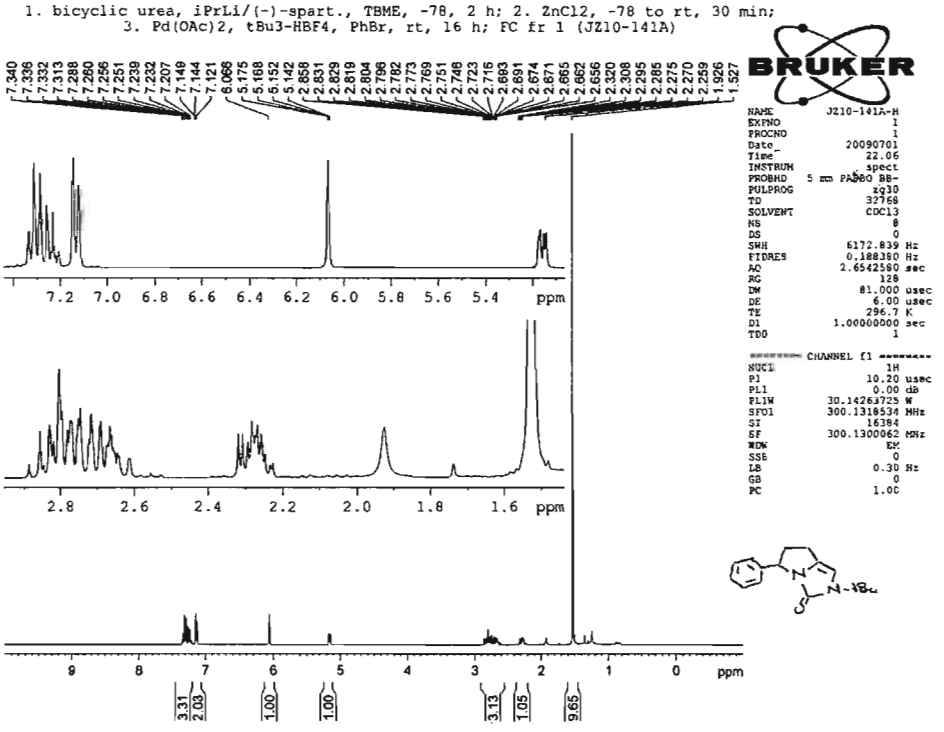

5.888
5.749
5.715
5.692
5.658
5.097
5.092
5.035
5.003
4.093
4.080
4.067
4.054
4.041
2.741
2.737
2.724
2.718
2.714
2.701
2.615
2.611
2.587
2.564
2.558
2.552
2.547
2.541
2.537
2.523
2.519
2.442
2.417
2.401
2.389
2.387
2.376
2.364
2.347
2.339
2.095
2.080
2.067
2.051
2.039
2.037
2.024
1.459
BRUKER
NAME sx6-137-h
EXPNO 1
PROCNO 1
Date_ 20090611
Time 11.42
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 45.3
DW 81.000 usec
DE 6.00 usec
TE 299.0 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PL1W 30.14263725 W
SFO1 300.1318534 MHz
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
C14H22N2O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.99
2.06
0.98
1.04
1.94
2.25
1.07
9.46

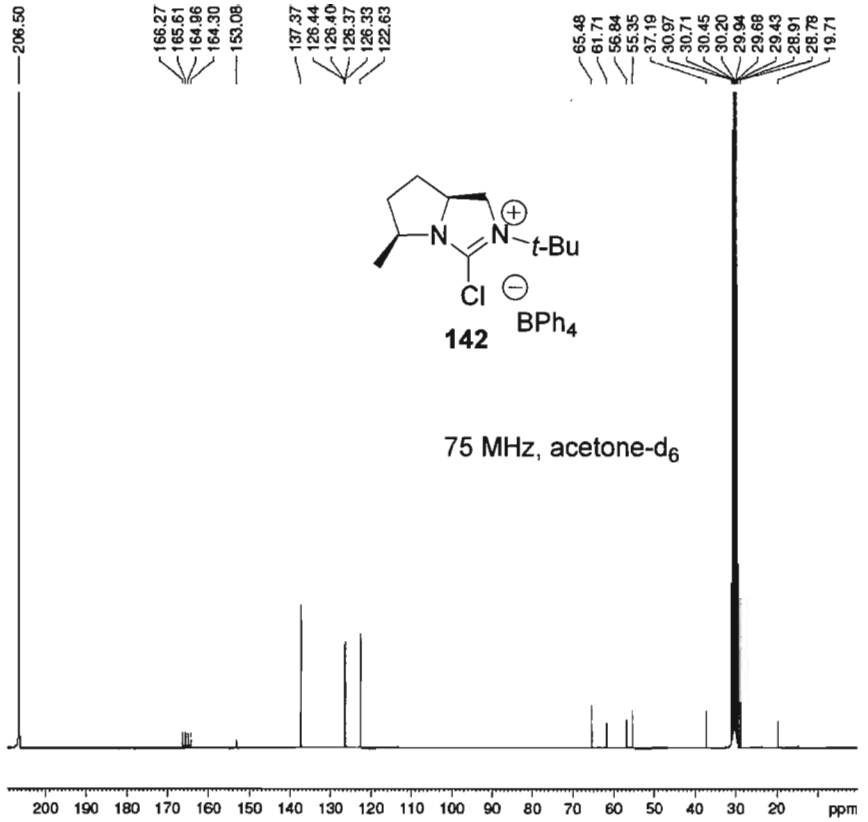

150.06
125.10
98.64
77.42
78.99
76.57
54.35
41.36
33.57
28.30
24.85
-9.77
Me3Sn
N
N
t-Bu
O
132
75 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

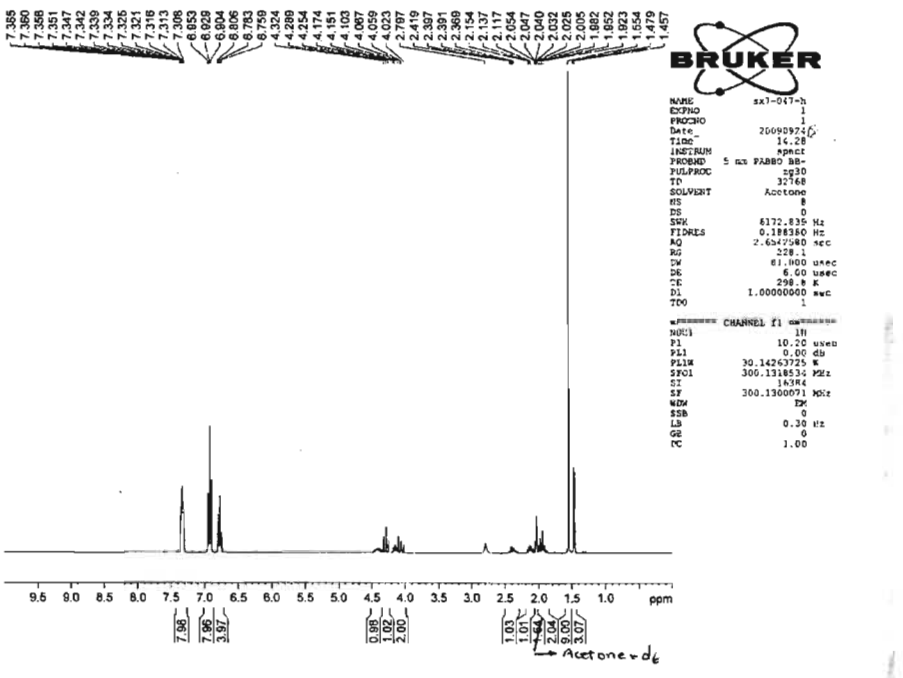

7.260
5.962
5.957
5.954
3.484
3.481
3.452
3.429
2.659
2.654
2.638
2.630
2.624
2.612
2.606
2.601
2.587
2.576
2.565
2.560
2.553
2.541
2.536
2.530
2.523
2.517
2.512
2.500
2.489
2.476
2.321
2.286
2.280
BRUKER
0.159
NAME sx7-023-h
EXPNO 2
PROCNO 1
Date_ 20090901
Time 10.03
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 64
DW 81.000 usec
DE 6.00 usec
TE 296.0 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PL1W 30.14263725 W
SFO1 300.1318534 MHz
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
3.18
0.97
9.60
7.78

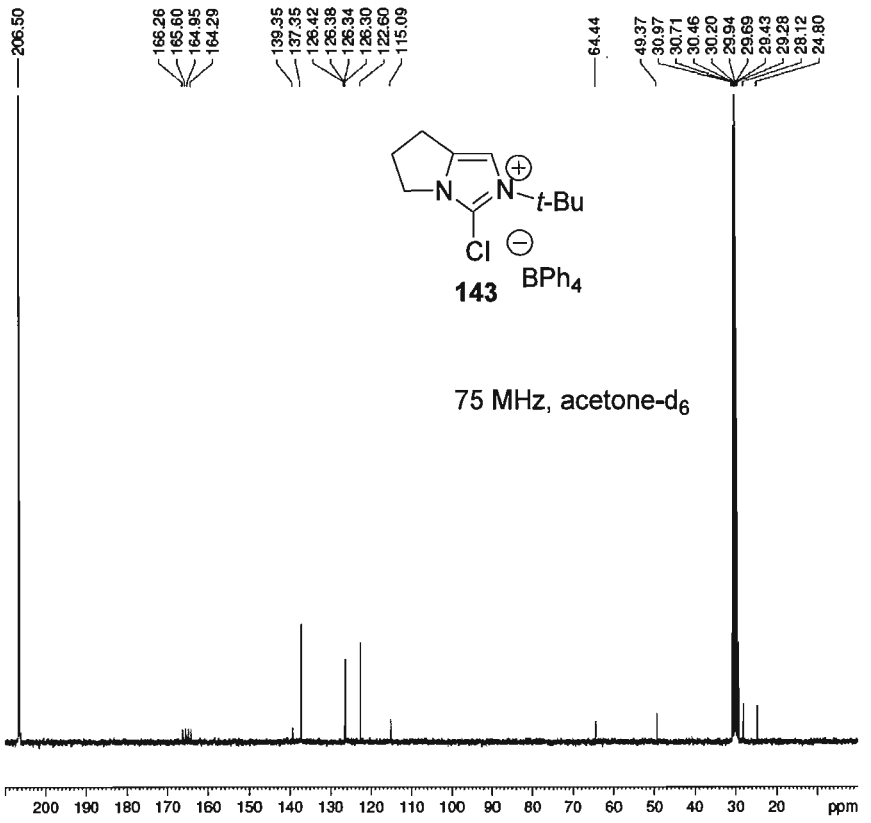


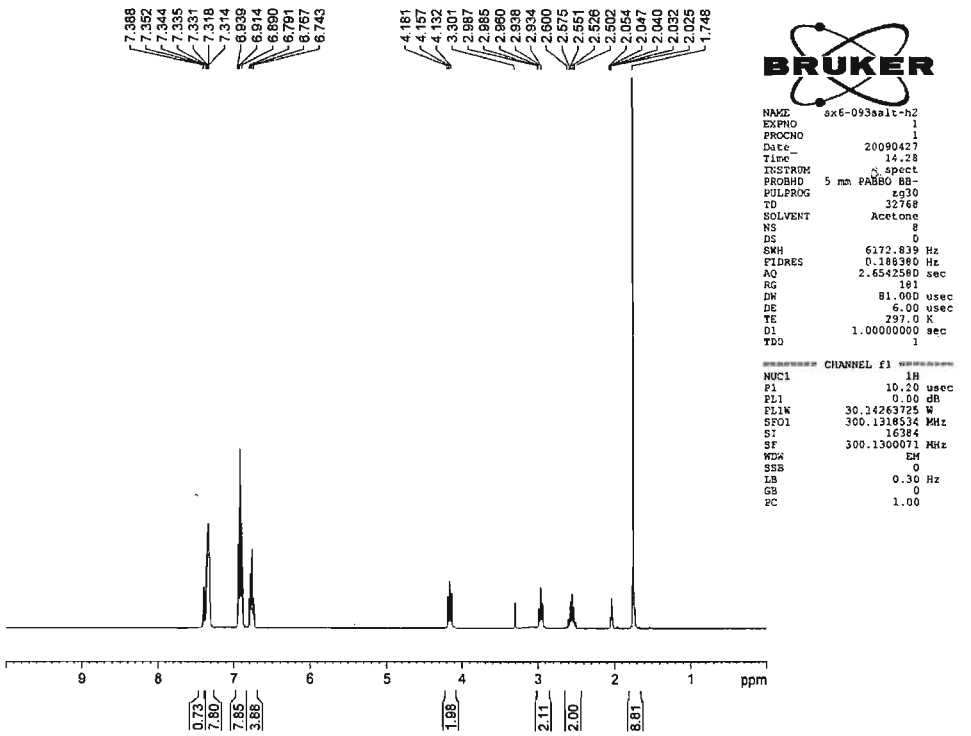
1. bicyclic urea, iPrLi/(-)-spart., TBME, -78, 2 h; 2. ZnCl2, -78 to rt, 30 min;
3. Pd(OAc)2, tBu3-HBF4, PhBr, rt, 16 h; FC fr 1 (JZ10-141A)

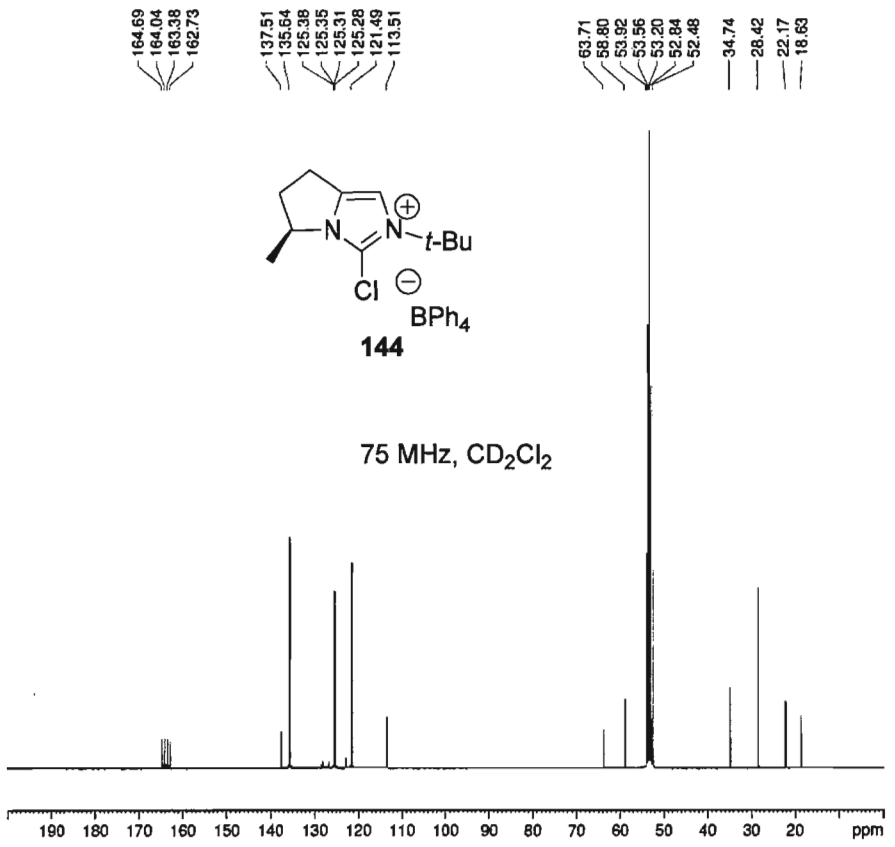


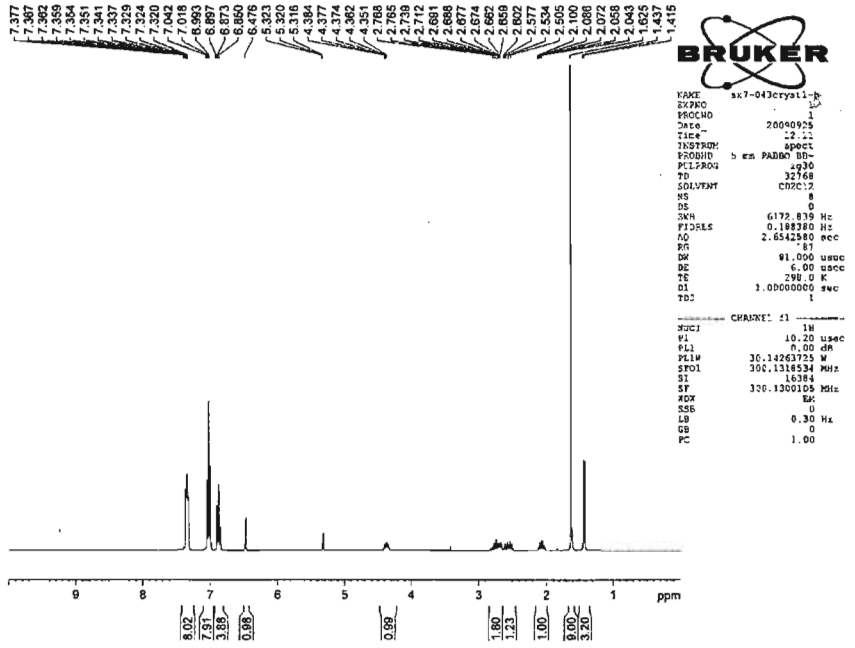

206.50
166.27
165.61
164.96
164.30
153.08
137.37
126.44
126.40
126.37
126.33
122.63
65.48
61.71
56.84
55.35
37.19
30.97
30.71
30.45
30.20
29.94
29.68
29.43
28.91
28.78
19.71
t-Bu
Cl
BPh4
142
75 MHz, acetone-d6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

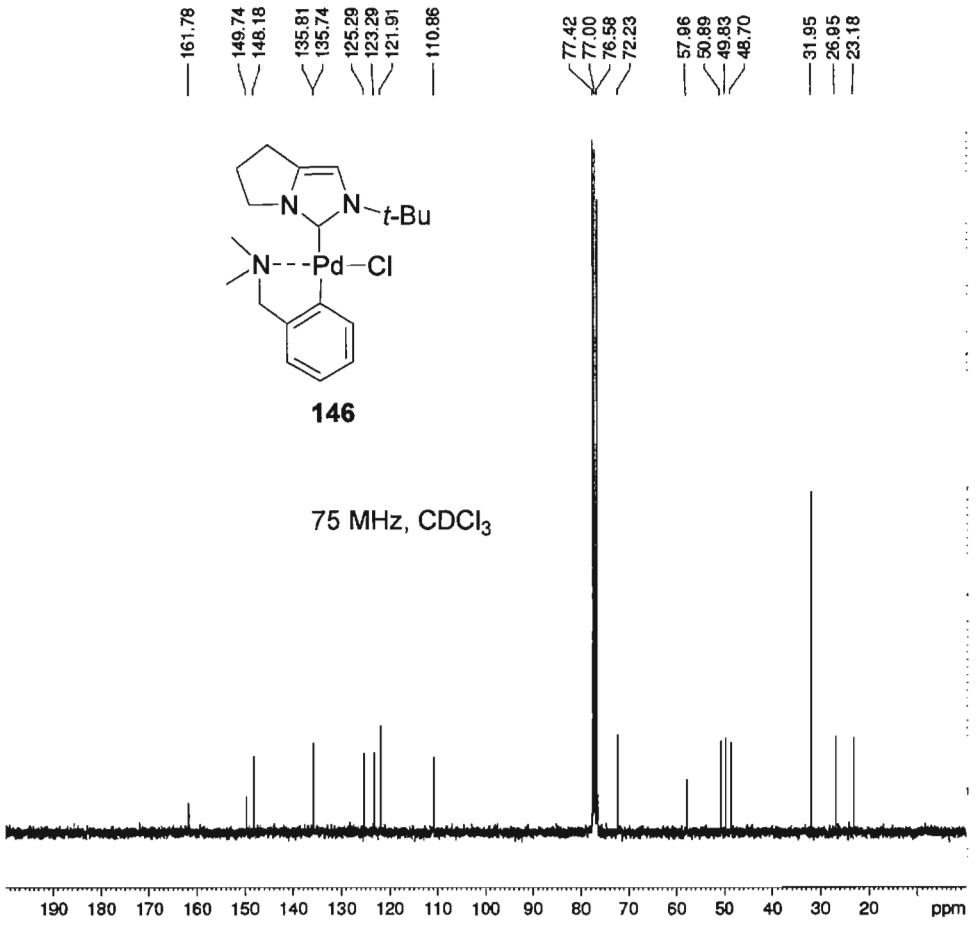

7.385
7.360
7.356
7.351
7.347
7.342
7.339
7.334
7.326
7.321
7.316
7.313
7.308
6.853
6.829
6.804
6.806
6.783
6.759
4.324
4.289
4.254
4.174
4.151
4.103
4.067
4.059
4.023
2.797
2.419
2.387
2.391
2.369
2.154
2.137
2.117
2.054
2.047
2.040
2.032
2.025
2.005
1.982
1.952
1.923
1.554
1.479
1.457
BRUKER
NAME sx7-047-h
EXPNO 1
PROCNO 1
Date_ 20090924
Time 14.28
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT Acetone
NS 8
DS 0
SWH 6172.835 Hz
FIDRES 0.188380 Hz
AQ 2.6547580 sec
RG 228.1
DW 81.000 usec
DE 6.00 usec
TE 298.8 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PL1W 30.14263725 W
SFO1 300.1318534 MHz
SI 16384
SF 300.1300071 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
7.98
7.96
3.97
0.99
1.02
2.00
1.03
1.01
1.44
2.04
9.00
3.07
Acetone-d6

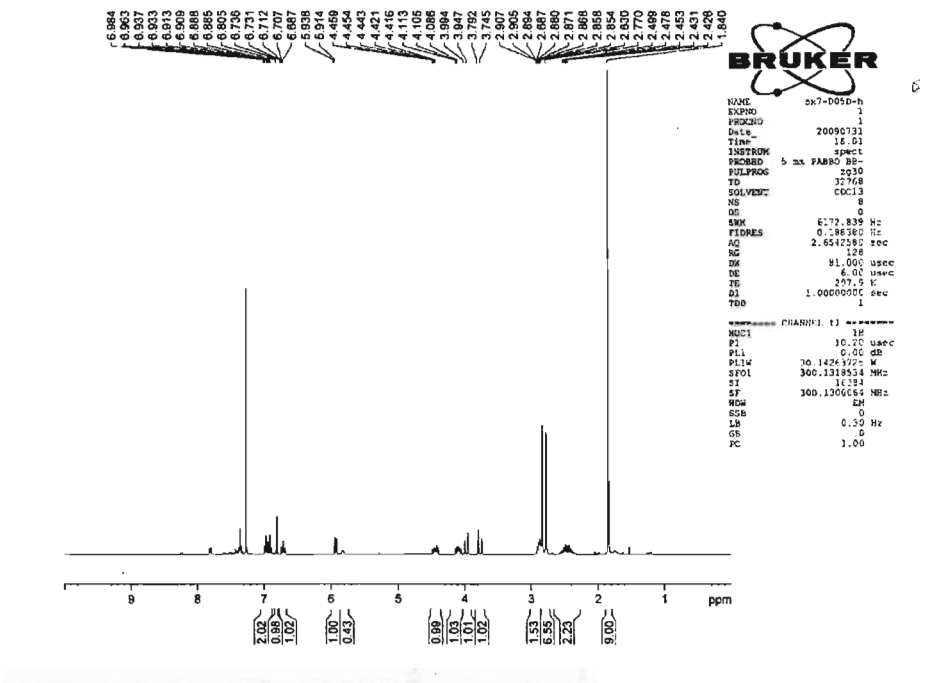

206.50
166.26
165.60
164.95
164.29
139.35
137.35
126.42
126.38
126.34
126.30
122.60
115.09
64.44
49.37
30.97
30.71
30.46
30.20
29.94
29.69
29.43
29.28
28.12
24.80
t-Bu
Cl
BPh4
143
75 MHz, acetone-d6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

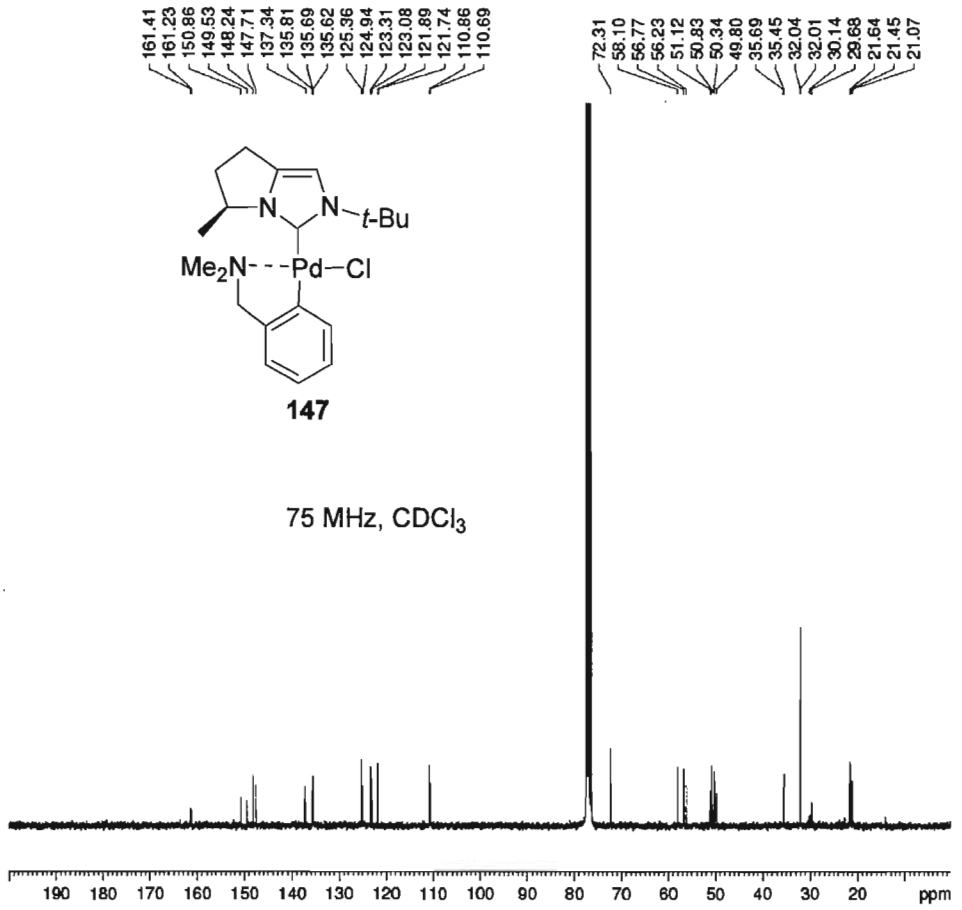

7.388
7.352
7.344
7.335
7.331
7.318
7.314
6.939
6.914
6.890
6.791
6.767
6.743
4.161
4.157
4.132
3.301
2.987
2.985
2.960
2.938
2.934
2.600
2.575
2.551
2.526
2.502
2.054
2.047
2.040
2.032
2.025
1.748
BRUKER
NAME sx6-093salt-h2
EXPNO 1
PROCNO 1
Date_ 20090427
Time 14.28
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT Acetone
NS 8
DS 0
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 101
DW 81.000 usec
DE 6.00 usec
TE 297.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PL1W 30.14263725 W
SFO1 300.1318534 MHz
SI 16384
SF 300.1300071 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9 8 7 6 5 4 3 2 1 ppm
0.73
7.80
7.85
3.88
1.98
2.11
2.00
8.81

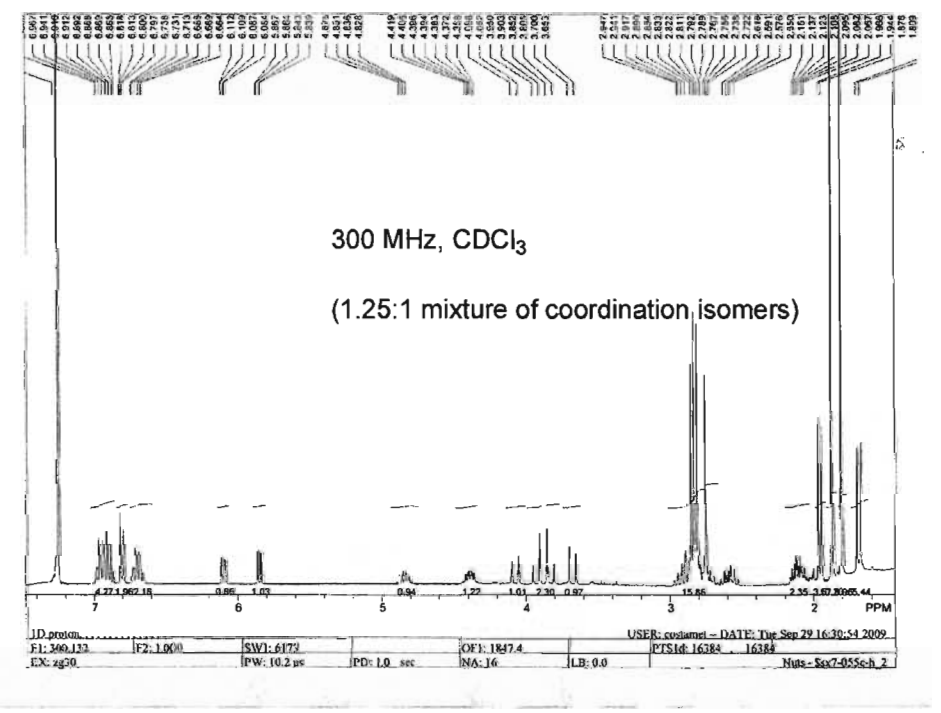

164.69
164.04
163.38
162.73
137.51
135.64
125.38
125.35
125.31
125.28
121.49
113.51
63.71
58.80
53.92
53.56
53.20
52.84
52.48
34.74
28.42
22.17
18.63
t-Bu
Cl
BPh4
144
75 MHz, CD2Cl2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

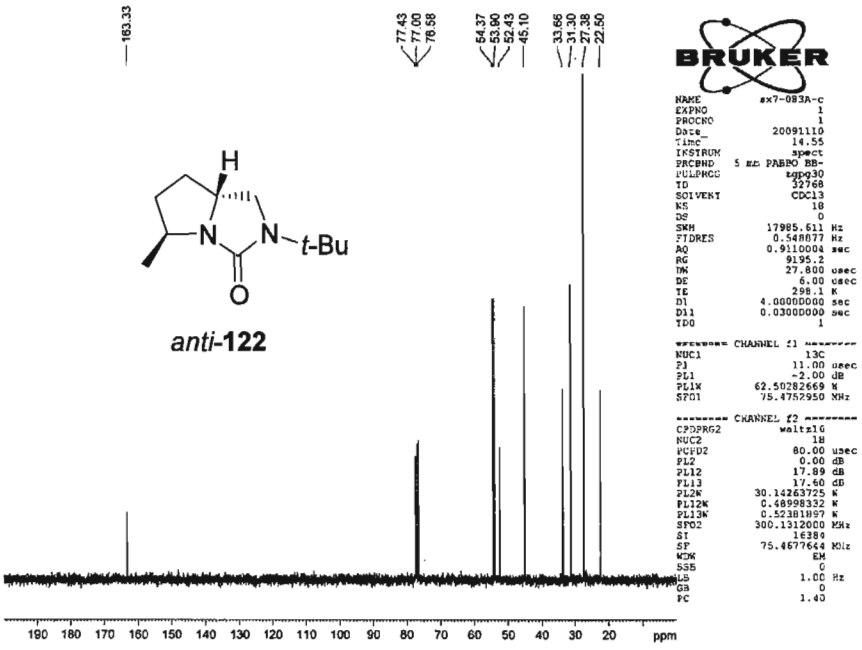

7.377
7.367
7.362
7.359
7.354
7.351
7.341
7.337
7.329
7.324
7.320
7.042
7.018
6.993
6.897
6.873
6.860
6.476
5.823
5.320
5.316
4.384
4.377
4.374
4.362
4.351
2.788
2.785
2.739
2.712
2.691
2.688
2.677
2.674
2.662
2.659
2.602
2.577
2.534
2.505
2.100
2.086
2.072
2.058
2.043
1.625
1.437
1.415
BRUKER
9 8 7 6 5 4 3 2 1 ppm
8.02
7.91
3.86
0.98
0.99
1.80
1.23
1.00
9.00
5.20

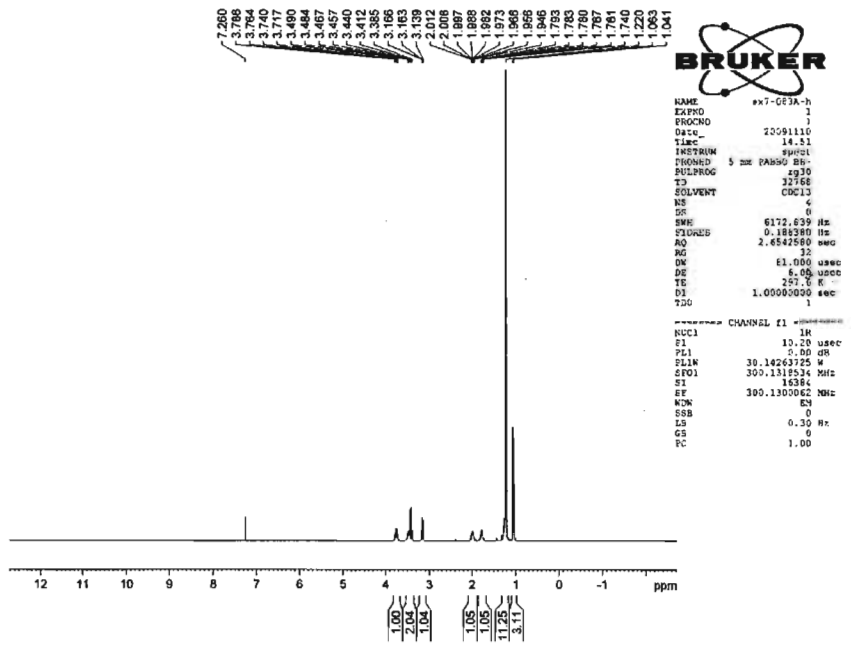

161.78
149.74
148.18
135.81
135.74
125.29
123.29
121.91
110.86
77.42
77.00
76.58
72.23
57.96
50.89
49.83
48.70
31.95
26.95
23.18
N
N
t-Bu
N---Pd—Cl
146
75 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


BRUKER
NAME sk7-D05D-h
EXPNO 1
PROCNO 1
Date_ 20090731
Time 16.01
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 6172.839 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 128
DW 81.000 usec
DE 6.00 usec
TE 297.9 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PL1W 30.14263775 W
SFO1 300.1318534 MHz
SI 16384
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9 8 7 6 5 4 3 2 1 ppm
2.02 0.98 1.02 1.00 0.43 0.98 1.03 1.01 1.02 1.53 6.55 2.23 9.00

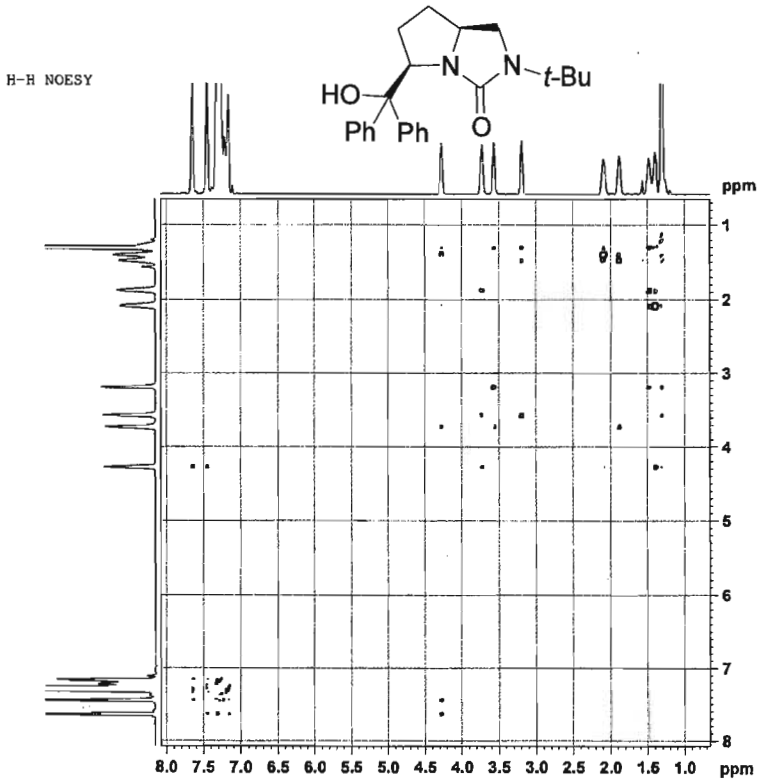

161.41
161.23
150.86
149.53
148.24
147.71
137.34
135.81
135.69
135.62
125.36
124.94
123.31
123.08
121.89
121.74
110.86
110.69
72.31
58.10
56.77
56.23
51.12
50.83
50.34
49.80
35.69
35.45
32.04
32.01
30.14
29.68
21.64
21.45
21.07
N
N
t-Bu
Me2N
Pd
Cl
147
75 MHz, CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

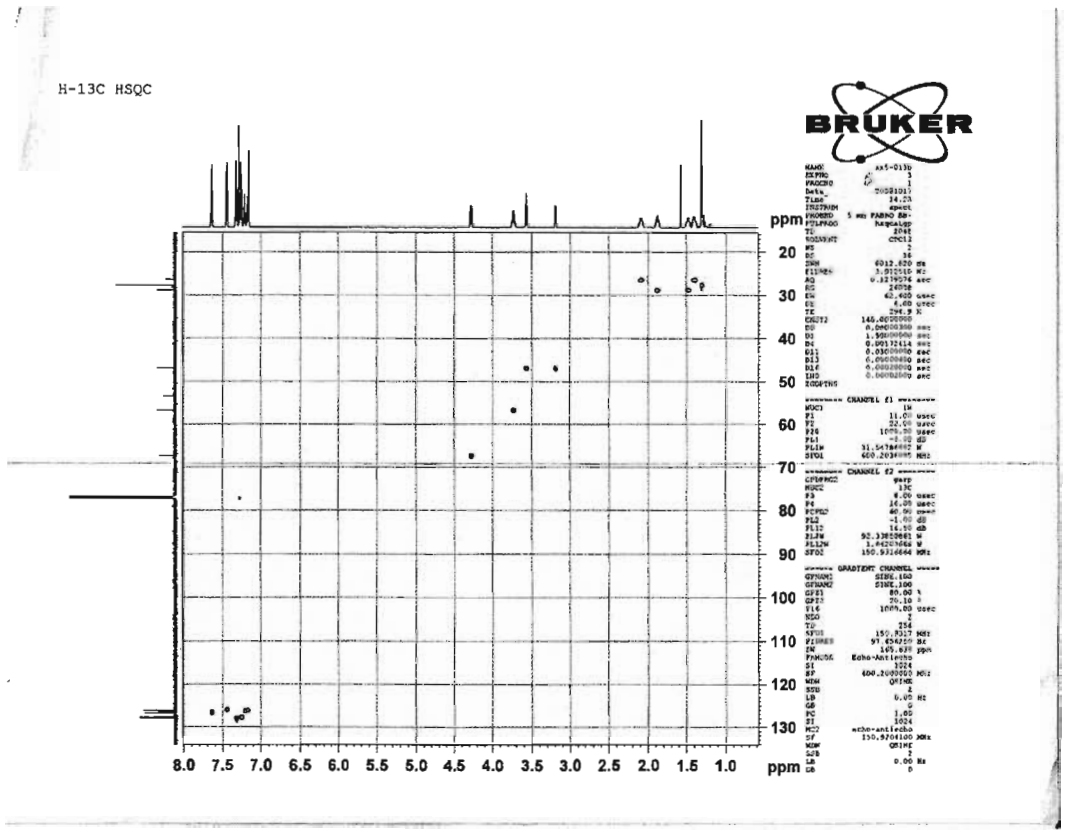

300 MHz, CDCl3
(1.25:1 mixture of coordination isomers)
7
6
5
4
3
2
PPM
1D proton
F1: 300.133
F2: 1.000
SW1: 6173
PW: 10.2 µs
PD: 1.0 sec
OF1: 1847.4
NA: 16
PTS1d: 16384 16384
LB: 0.0
EX: zg30
USER: coolamet – DATE: Tue Sep 29 16:30:54 2009
Nuts - Sep7-055c-h_2


163.33
77.43
77.00
76.58
64.37
53.90
52.43
45.10
33.66
31.30
27.38
22.50
H
N
N
t-Bu
O
anti-122
BRUKER
NAME sx7-083A-c
EXPNO 1
PROCNO 1
Date_ 20091110
Time_ 14.55
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 18
DS 0
SWH 17985.611 Hz
FIDRES 0.548877 Hz
AQ 0.9110004 sec
RG 9195.2
DW 27.800 usec
DE 6.00 usec
TE 298.1 K
D1 4.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 11.00 usec
PL1 -2.00 dB
PL1W 62.50282669 W
SFO1 75.4752950 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 17.89 dB
PL13 17.60 dB
PL2W 30.14263725 W
PL12W 0.48998332 W
PL13W 0.52381897 W
SFO2 300.1312000 MHz
SI 16384
SF 75.4677644 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

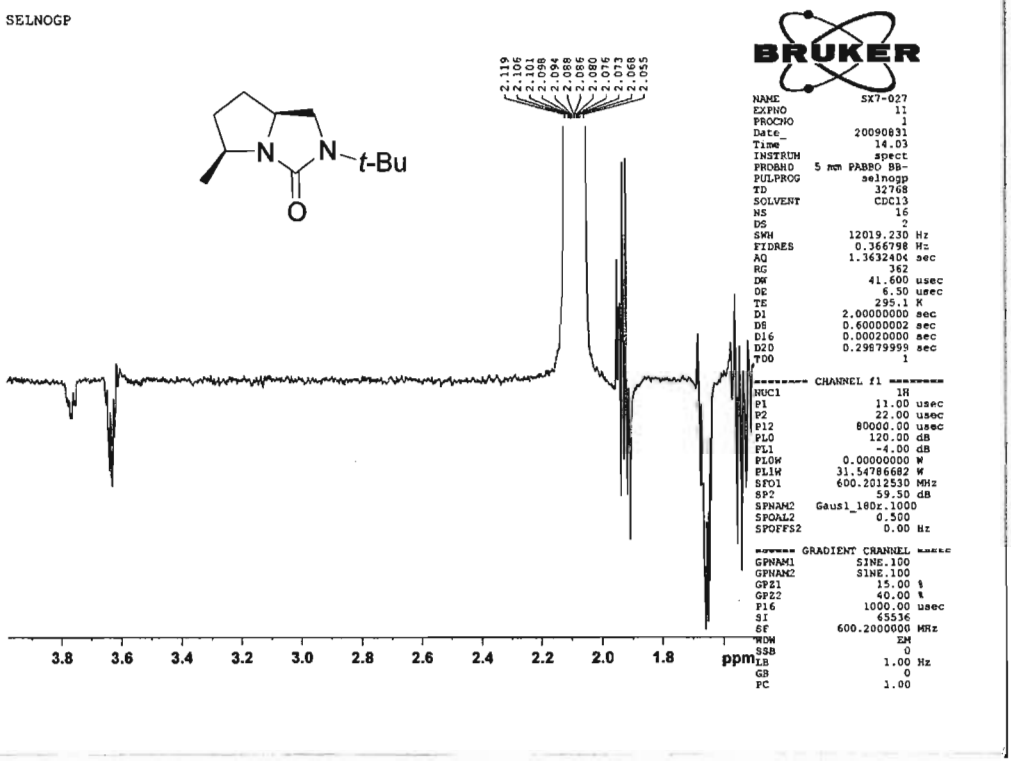

7.260
3.786
3.764
3.740
3.717
3.490
3.484
3.467
3.457
3.440
3.412
3.385
3.166
3.163
3.139
2.012
2.008
1.987
1.988
1.982
1.973
1.968
1.958
1.946
1.793
1.783
1.780
1.767
1.761
1.740
1.220
1.063
1.041
BRUKER
NAME sx7-083A-h
EXPNO 1
PROCNO 1
Date_ 20091110
Time_ 14.51
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 6172.639 Hz
FIDRES 0.188380 Hz
AQ 2.6542580 sec
RG 32
DW 81.000 usec
DE 6.00 usec
TE 297.0 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.20 usec
PL1 0.00 dB
PL1W 30.14263725 W
SFO1 300.1312534 MHz
SI 16384
SF 300.1300062 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
1.00
2.04
1.04
1.05
1.05
11.25
3.11

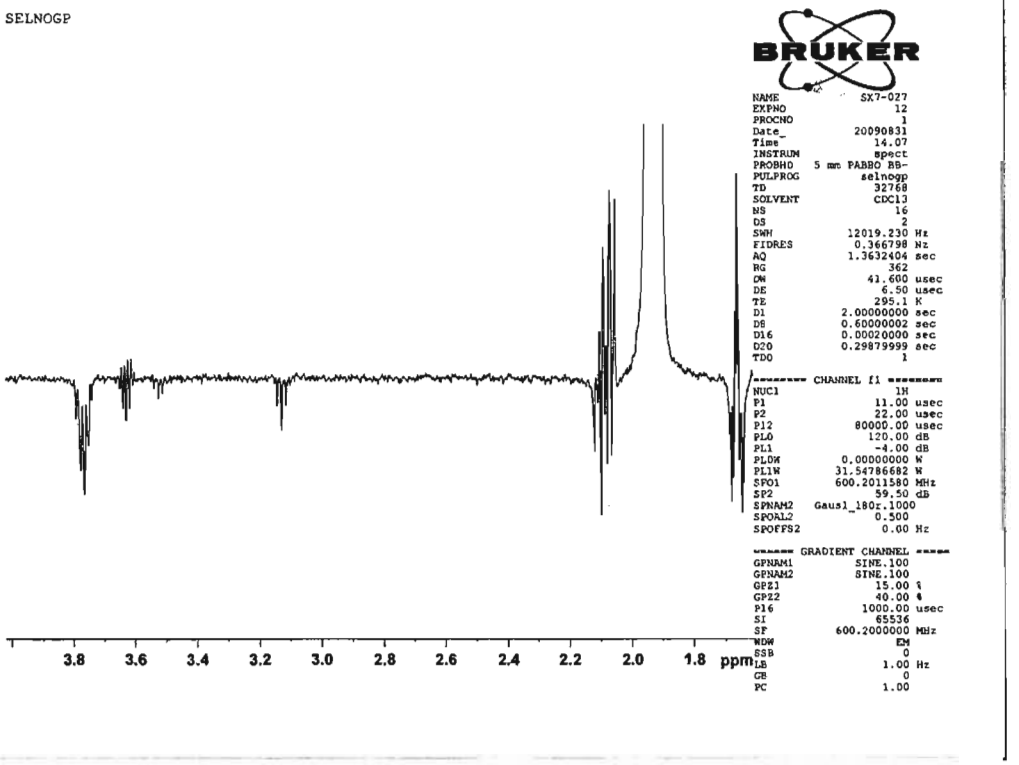
NOESY and HSQC for **121**



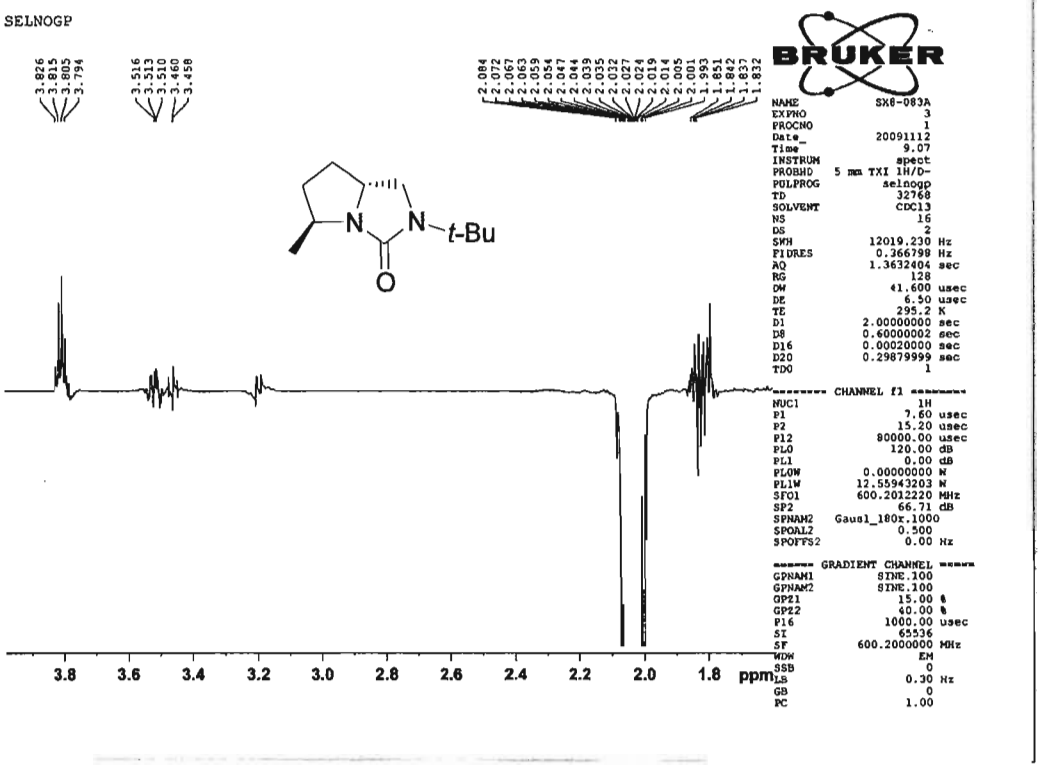


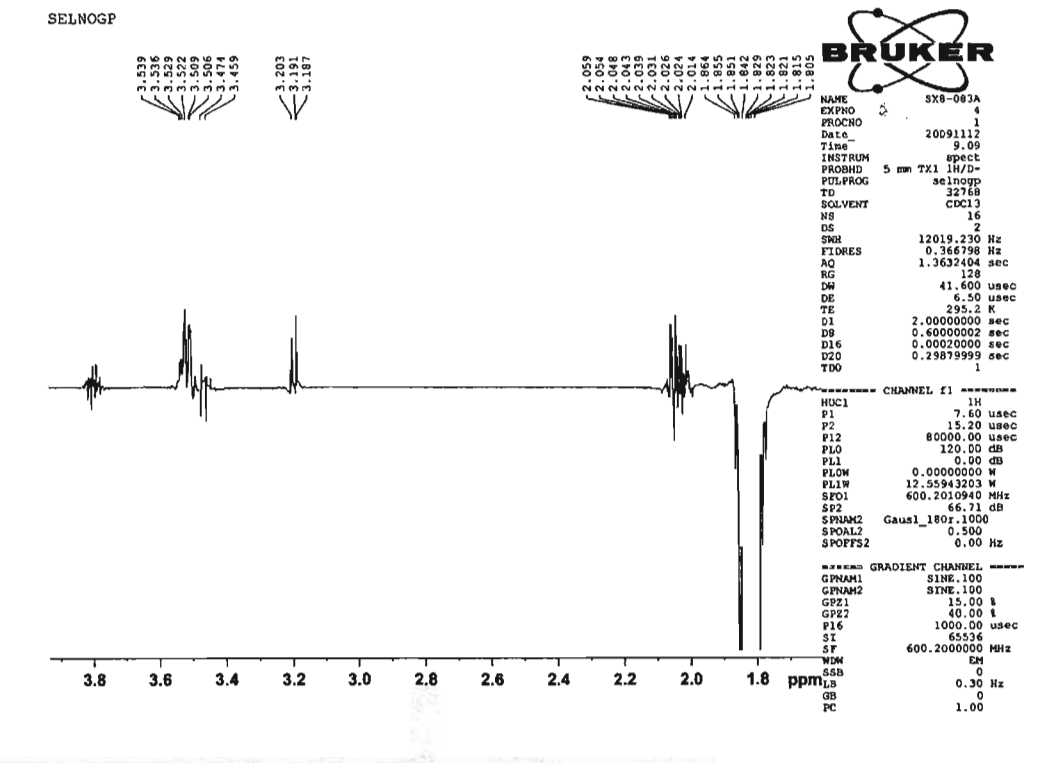
1D-NOEs for *syn*-**122**



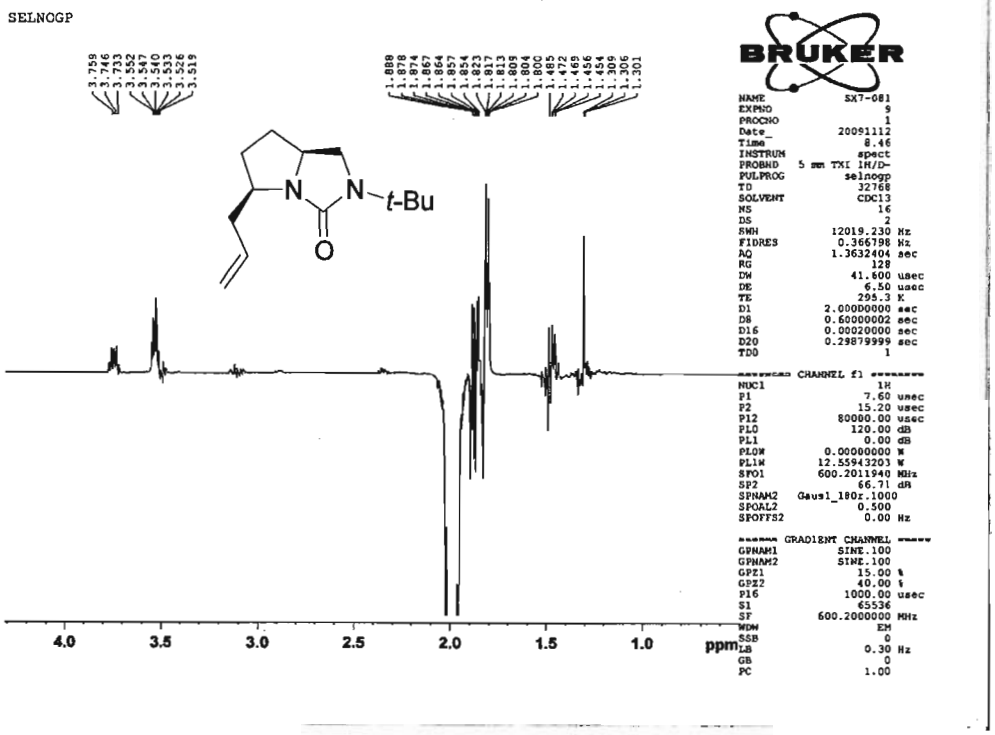


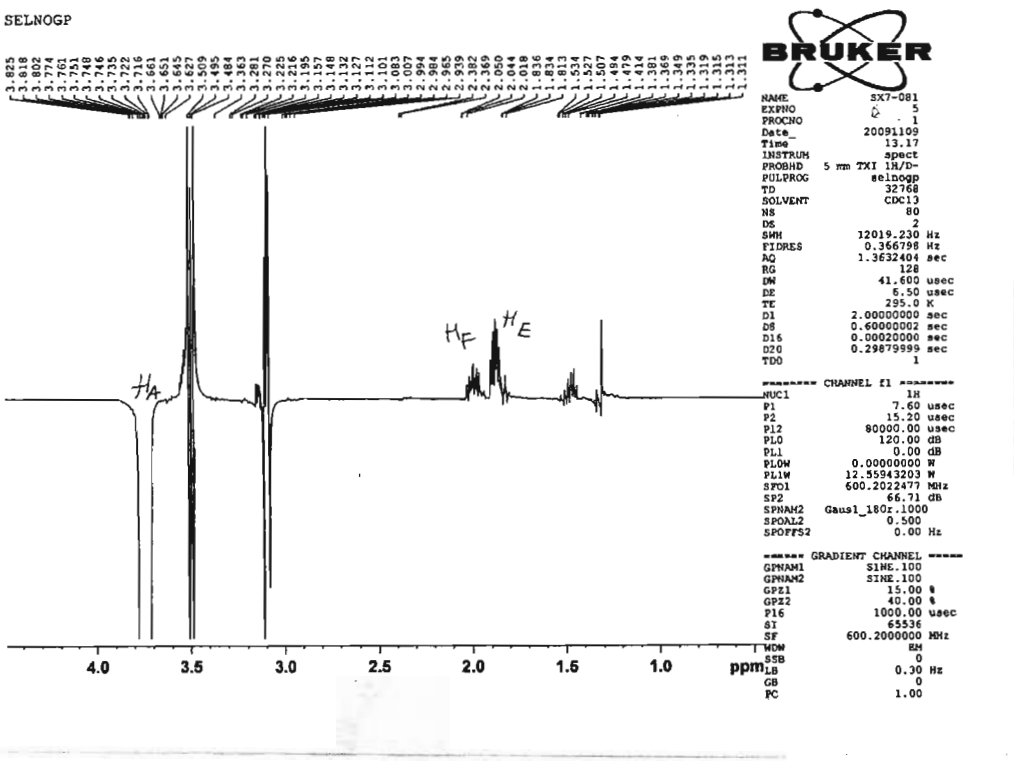
1D-NOEs for *anti*-**122**



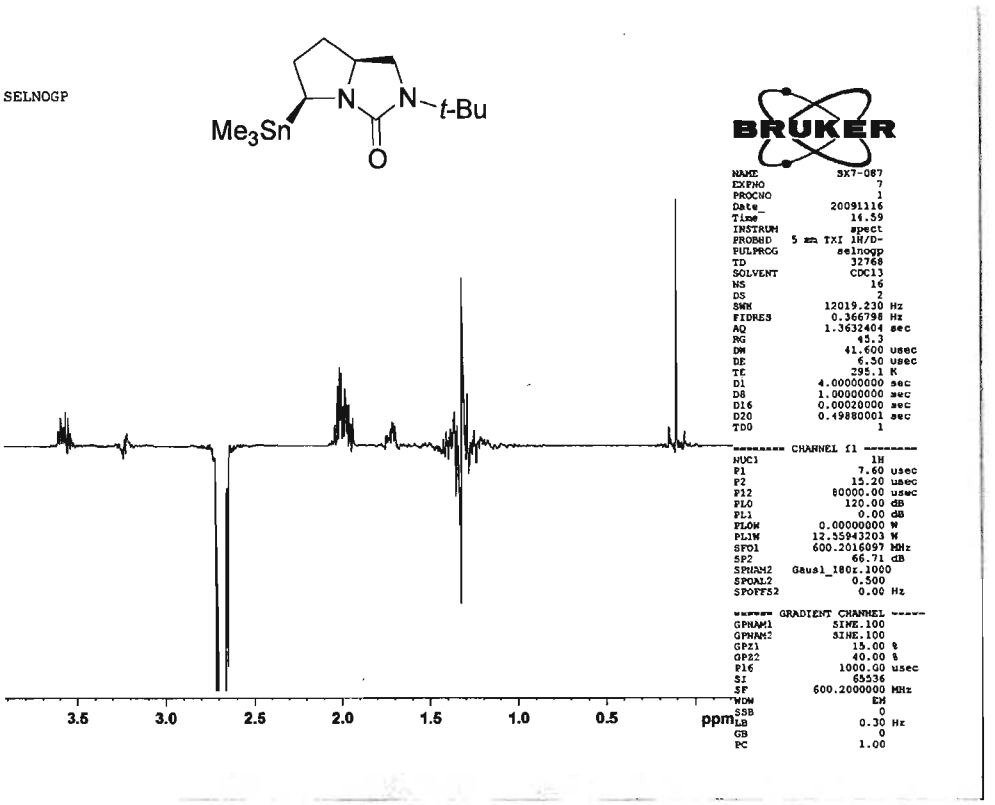


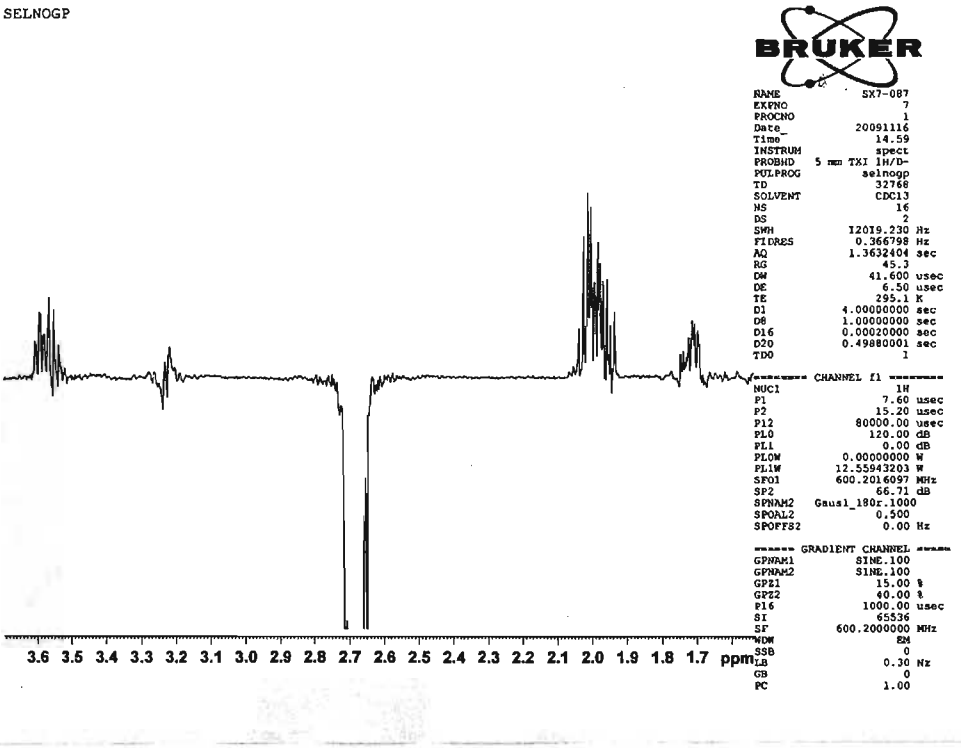
1-D NOEs for **123**

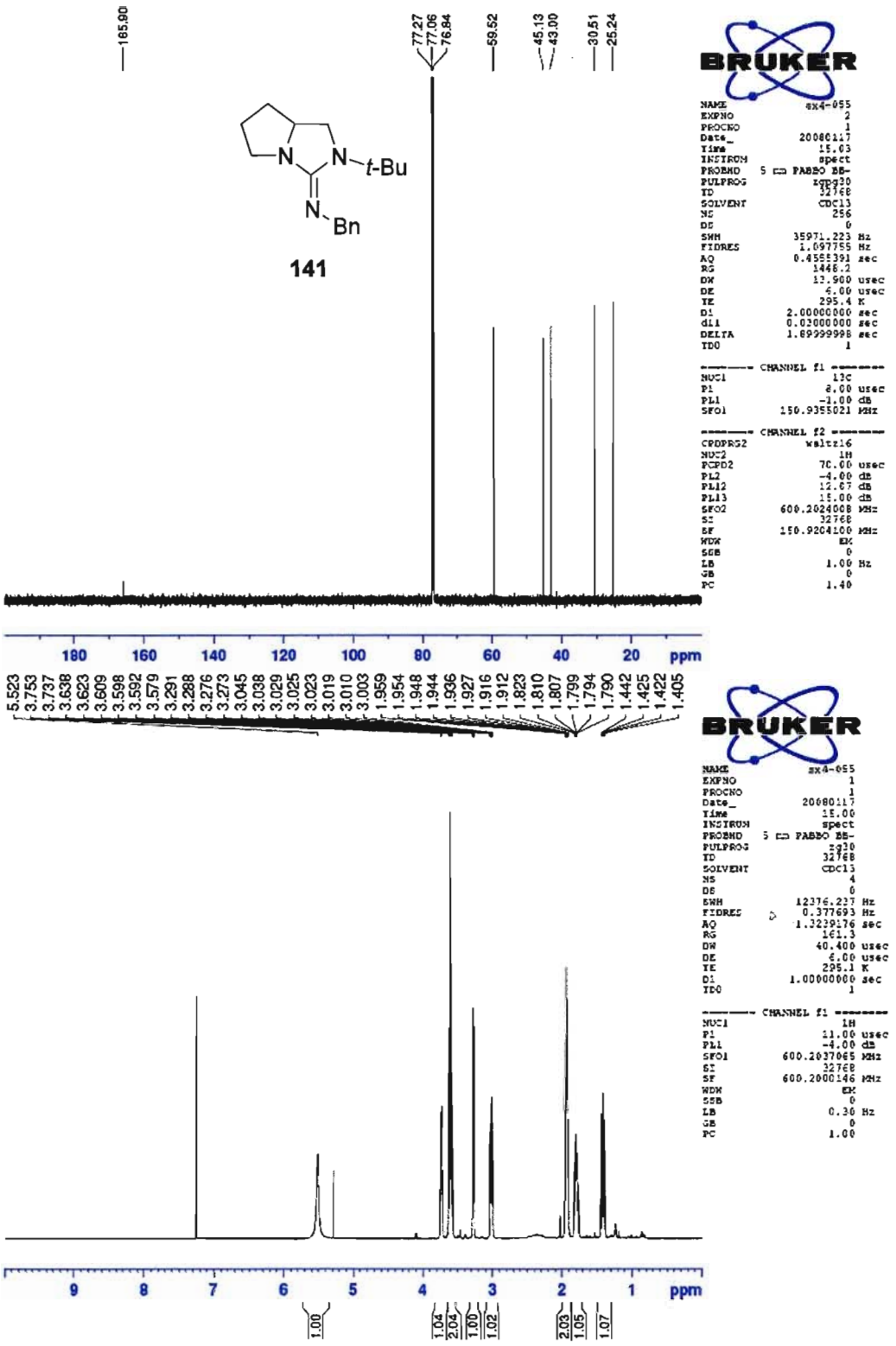


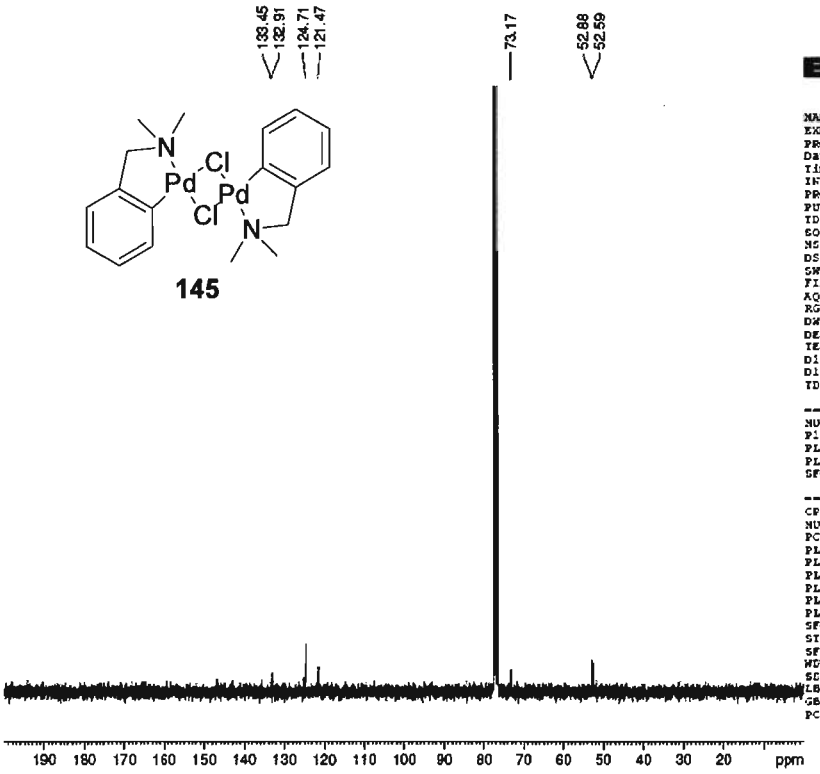


1-D NOEs for **122**



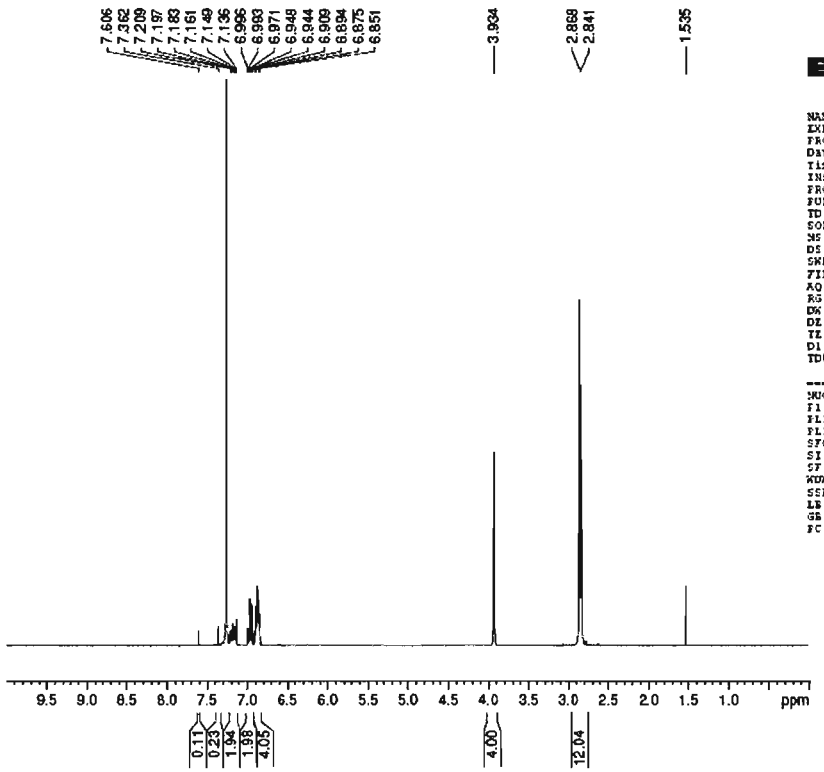



185.90
77.27
77.06
76.84
59.52
45.13
43.00
30.51
25.24
N
N
t-Bu
N
Bn
141
BRUKER
NAME ex4-055
EXPNO 2
PROCNO 1
Date_ 20080117
Time 15.03
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 256
DS 0
SWH 35971.223 Hz
FIDRES 1.097755 Hz
AQ 0.4555391 sec
RG 1446.2
DW 13.900 usec
DE 6.00 usec
TE 295.4 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 8.00 usec
PL1 -1.00 dB
SFO1 150.9355021 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 70.00 usec
PL2 -4.00 dB
PL12 12.67 dB
PL13 15.00 dB
SFO2 600.2024008 MHz
SI 32768
SF 150.9204100 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180 160 140 120 100 80 60 40 20 ppm
5.523 3.753 3.737 3.638 3.623 3.609 3.598 3.592 3.579 3.291 3.288 3.276 3.273 3.045 3.038 3.029 3.025 3.023 3.019 3.010 3.003 1.959 1.954 1.948 1.944 1.936 1.927 1.916 1.912 1.823 1.810 1.807 1.799 1.794 1.790 1.442 1.425 1.422 1.405
BRUKER
NAME ex4-055
EXPNO 1
PROCNO 1
Date_ 20080117
Time 15.00
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 4
DS 0
SWH 12376.237 Hz
FIDRES 0.377693 Hz
AQ 1.3229176 sec
RG 161.3
DW 40.400 usec
DE 6.00 usec
TE 295.1 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 11.00 usec
PL1 -4.00 dB
SFO1 600.2037065 MHz
SI 32768
SF 600.2000146 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9 8 7 6 5 4 3 2 1 ppm
1.00 1.04 2.04 1.00 1.02 2.03 1.05 1.07



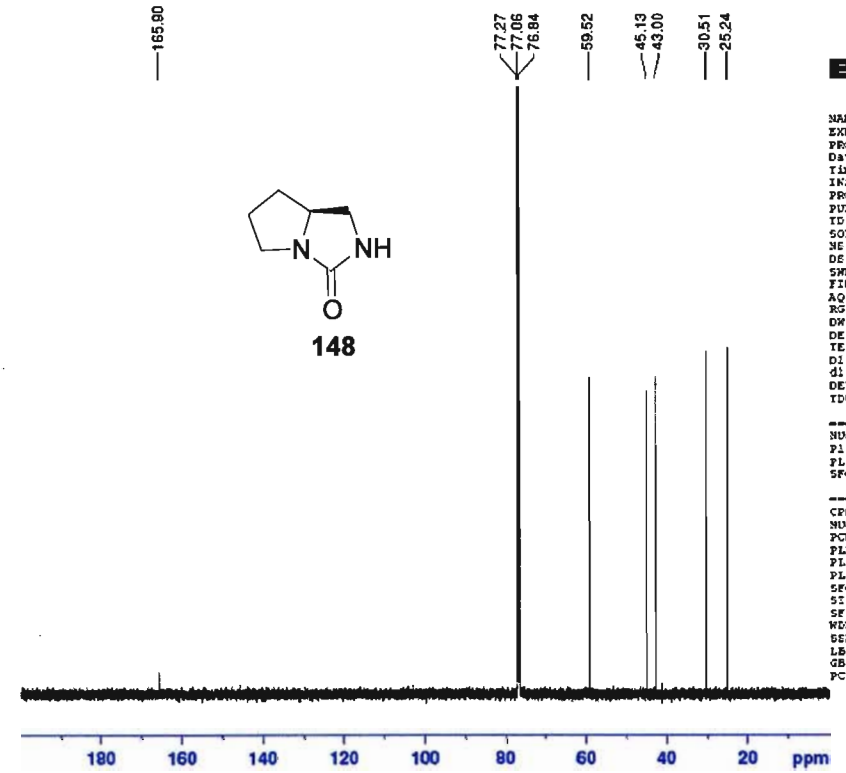
BRUKER

```
NAME          sx7-003cryst1-c
EXPNO                       1
PROCNO                      1
Date_              20090729
Time                   19.59
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG              zgpg30
TD                    32768
SOLVENT               CDCl3
NS                      256
DS                        0
SWH              17985.611 Hz
FIDRES            0.548877 Hz
AQ                0.9110004 sec
RG                   2580.3
DW                  27.800 usec
DE                   6.00 usec
TE                  298.1 K
D1             4.00000000 sec
D11            0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                    11.00 usec
PL1                   -2.00 dB
PL1W           62.50282669 W
SFO1           75.4752950 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2                 80.00 usec
PL2                    0.00 dB
PL12                  17.89 dB
PL13                  17.60 dB
PL2W           30.14263725 W
PL12W           0.48996332 W
PL13W           0.52381827 W
SFO2           300.1312000 MHz
SI                     16384
SF             75.4677490 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```



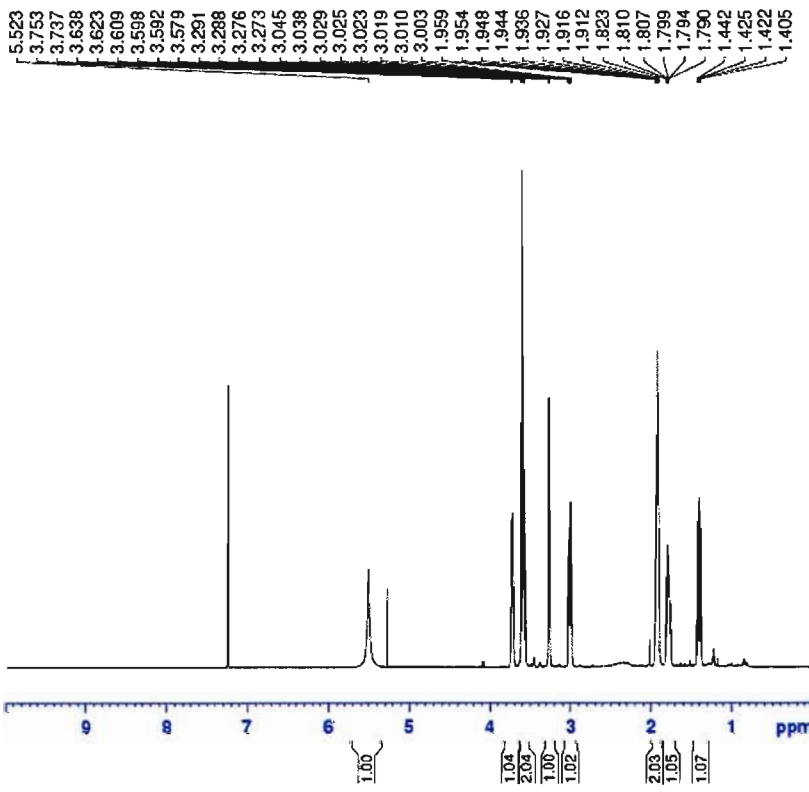
BRUKER

```
NAME          sx7-003cryst1-h
EXPNO                       1
PROCNO                      1
Date_              20090729
Time                   19.52
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                    32768
SOLVENT               CDCl3
NS                        8
DS                        0
SWH               6172.839 Hz
FIDRES            0.188380 Hz
AQ                2.6542580 sec
RG                   456.1
DW                  81.000 usec
DE                   6.00 usec
TE                  297.4 K
D1             1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    1H
P1                    10.20 usec
PL1                    0.00 dB
PL1W           30.14263725 W
SFO1           300.1318534 MHz
SI                     16384
SF             300.1300062 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```



BRUKER

NAME	sx4-055
EXPNO	2
PROCNO	1
Date_	20080117
Time	15.03
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	256
DS	0
SWH	35971.223 Hz
FIDRES	1.097755 Hz
AQ	0.4555391 sec
RG	1448.2
DW	13.900 usec
DE	6.00 usec
TE	295.4 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	8.00 usec
PL1	-1.00 dB
SFO1	150.9355021 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	70.00 usec
PL2	-4.00 dB
PL12	12.07 dB
PL13	15.00 dB
SFO2	600.2024008 MHz
SI	32768
SF	150.9204100 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



BRUKER

NAME	sx4-055
EXPNO	1
PROCNO	1
Date_	20080117
Time	15.00
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	4
DS	0
SWH	12376.237 Hz
FIDRES	0.377693 Hz
AQ	1.3229176 sec
RG	161.3
DW	40.400 usec
DE	6.00 usec
TE	295.1 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	11.00 usec
PL1	-4.00 dB
SFO1	600.2037065 MHz
SI	32768
SF	600.2000146 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00